THE MEDICAL CLINICS OF NORTH AMERICA

NOVEMBER 1976

GERIATRIC MEDICINE

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SYMPOSIUM ON
GERIATRIC MEDICINE

Sandor A. Friedman, M.D., and
Francis U. Steinheber, M.D., *Guest Editors*

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Contributors

BARBARA A. L. BEASLEY, M.D., Associative Chief of Neurology, U.S. Public Health Service Hospital, Staten Island; Associate Professor of Neurology, State University of New York, Downstate Medical Center

PATRICK R. BERGEVIN, M.D., Chief, Oncology Division, Coney Island Hospital; Assistant Professor of Medicine, State University of New York, Downstate Medical Center

HARRY BIENENSTOCK, M.D., Chief, Rheumatology Division, Coney Island Hospital and Long Island College Hospital; Assistant Attending Physician, The Hospital for Special Surgery; Assistant Clinical Professor of Medicine, Cornell University Medical College

SANTI DHAR, M.D., Chief, Pulmonary Disease Division, Coney Island Hospital

GLORIA FERNANDEZ, M.D., Director of the Blood Bank, Coney Island Hospital; Instructor in Medicine, State University of New York, Downstate Medical Center

K. RANJIT FERNANDO, M.D., Fellow in Rheumatology, Long Island College Hospital and Coney Island Hospital

DONALD H. FORD, Ph.D., Professor of Anatomy, State University of New York, Downstate Medical Center

SANDOR A. FRIEDMAN, M.D., F.A.C.P., Chief of Medical Services and Chief of Peripheral Vascular Disease Division, Coney Island Hospital; Associate Professor of Medicine, State University of New York, Downstate Medical Center

JULES L. GLADSTONE, M.D., Chief, Division of Infectious Disease, Coney Island Hospital; Assistant Professor of Medicine, State University of New York, Downstate Medical Center

SEYMOUR M. GLICK, M.D., Professor and Chairman, Department of Medicine, Ben Gurion University of the Negev; Health Sciences Center; Chief, Division of Medicine, Soroka University Hospital, Beersheva, Israel; Formerly Chief of Medical Services, Coney Island Hospital

LEWIS GLICKMAN, M.D., Assistant Professor of Psychiatry, Downstate Medical Center; Liaison Coordinator, Coney Island Hospital

ERNST GREIF, M.D., Chief, Cardiology Division, Coney Island Hospital; Assistant Professor, State University of New York, Downstate Medical Center

SHAFKAT HUSSAIN, M.D., Associate Chief of Hematology Division, Coney Island Hospital; Assistant Professor of Medicine, State University of New York, Downstate Medical Center

ROBOLGE A. K. LENORA, M.D., Fellow, Pulmonary Disease Division, Coney Island Hospital

MOHAN NARAYANAN, M.D., Gastroenterology Fellow, Gastroenterology Division, Coney Island Hospital

MOSSA NEJAT, M.D., Chief, Cardiac Catheterization Laboratory, Coney Island Hospital; Assistant Professor, Department of Medicine, State University of New York, Downstate Medical Center

ROSE RECCO, M.D., Physician-in-Charge of Antibiotic Surveillance Program, Coney Island Hospital; Instructor in Medicine, State University of New York, Downstate Medical Center

HERMAN ROSEN, M.D., F.A.C.P., Chief, Nephrology Division, Coney Island Hospital; Associate Professor of Clinical Medicine, State University of New York, Downstate Medical Center

JOEL M. SCHWARTZ, M.D., Chief of Hematology, Coney Island Hospital; Clinical Associate Professor of Medicine, State University of New York, Downstate Medical Center

BERNARD P. SHAGAN, M.D., Chief, Division of Endocrinology and Metabolism, Coney Island Hospital; Assistant Professor of Medicine, State University of New York, Downstate Medical Center

SUBRAMANIAM R. SHASTRI, M.D., Fellow, Pulmonary Disease Division, Coney Island Hospital

FRANCIS U. STEINHEBER, M.D., Chief of Gastroenterology Division, Coney Island Hospital; Instructor in Clinical Medicine, New York University School of Medicine

MARY WHEELER, M.D., Associate Chief of Endocrinology and Metabolic Division, Coney Island Hospital; Assistant Professor in Medicine, State University of New York, Downstate Medical Center

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Foreword

This issue of *Medical Clinics of North America* gives formal recognition to the unique and complex medical problems associated with aging.

Census data show that the elderly account for an increasingly higher percentage of the American population, a trend likely to continue during the next few decades. It is estimated that since 1970 the number of Americans over age 65 has increased from approximately 20 million to 23 million. By the year 2010, if current trends continue, 17 per cent of Americans will be 65 or older. The nation must address itself to the formidable social, economic, and health problems of our senior citizens.

It is impossible to say when old age begins. Aging is the sum of a host of gradual physiologic and emotional changes. Almost every organ loses functional capacity with age, but the rate is variable and is accelerated by environmental hazards and certain chronic diseases. On the whole, the elderly respond to systemic illness with relatively blunted inflammatory reactions, a higher threshold for pain, and more variability of signs and symptoms. The physiologic reasons for these clinical differences are not entirely clear, but loss of functional reserve is a key factor. Often it is the organ that has deteriorated most that is reponsible for clinical symptoms even if the acute pathology lies elsewhere. Another factor is the relatively sedentary existence of the elderly, a condition which may delay the appearance of cardiovascular and pulmonary symptoms until disease is far advanced.

Because Coney Island Hospital is located in an area with a very large aging population, the faculty of the Department of Medicine has acquired a vast experience in dealing with geriatric medical problems. We have seen constellations of signs and symptoms in response to disease that are at marked variance with standard textbook descriptions, and through the years, certain consistent patterns have become apparent. In this volume, we have attempted to share our experience and to provide a physiologic background for it, in the hope that we can offer some additional insight into the care of the elderly. Our emphasis is one of optimism. Aging does not have to follow a depressing, downhill course. Many medical complications associated with aging can be prevented or at least temporarily overcome so that the elderly may remain healthy enough to enjoy the fruits of their experience and maturity. Age should never be a barrier to appropriate investigation and treatment of any significant symptoms.

We are particularly grateful to several people who aided in the preparation of this volume. Mr. Abraham Lass, educational consultant to Coney Island Hospital, read each manuscript thoroughly and offered many valuable suggestions concerning organization and style. He prodded us away from medical obfuscation and toward clarity. Without the cooperation of our very busy office staff, this volume would not have been possible. Ms. Jeanette Kaplan made sure that the massive amount of paperwork flowed smoothly, as draft after draft of each manuscript surfaced. Ms. Edna Flug, Ms. Elayne Goldstein, and Ms. Nancy Mannion handled the gargantuan typing job accurately and expeditiously.

SANDOR A. FRIEDMAN, M.D.
FRANCIS U. STEINHEBER, M.D.
Guest Editors

Coney Island Hospital
2601 Ocean Parkway
Brooklyn, New York 11235

The Aging Heart

A Clinical Review

Moossa Nejat, M.D., and Ernst Greif, M.D.***

In any discussion of the aging process, the heart must assume a central position, since it is the failure of this organ to function effectively that leads to much of the chronic illness seen in the elderly. The deterioration of cardiac contractility with advancing age is set against a background of decreasing functional reserve in other major organs of the body. As a result, symptoms of heart disease may be preceded in many cases by the effects of regional circulatory failure. In fact, limitations imposed by loss of function elsewhere may actually prevent the emergence of specific cardiac symptoms. The purpose of this article is to explore the degenerative processes and the clinical manifestation of the aging heart.

In trying to understand cardiac disease in the elderly, one first examines the morphology of the heart, but this approach has not been very revealing. There is little specificity in the anatomic changes. The heart atrophies relatively little, and the only intracellular change is the deposition of a lipofuchsin pigment that does not seem to interfere with myocardial contractility. In general, histologic appearance depends on the amount and location of coronary atherosclerosis, which leads to myocardial fibrosis. Two rather specific findings that can be well correlated with clinical syndromes are the infiltration of amyloid between cardiac fibers and degenerative, calcific changes at the aortic valve. These will be discussed later.

The effects of age per se on cardiac performance are difficult to evaluate for several reasons. First, it is difficult to separate the role of coronary atherosclerosis from intrinsic changes within the myocardial fibers. Although atherosclerosis increases throughout one's lifetime, the amount of circulatory insufficiency at any given age is extremely variable. Secondly, the significance of changes in cardiac output is unclear. Resting cardiac output decreases 30 to 40% between the ages of 25 and 65, but this is not necessarily a reflection of decreased myocardial capac-

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*Chief, Cardiac Catheterization Laboratory, Coney Island Hospital; Assistant Professor, Department of Medicine, State University of New York, Downstate Medical Center, Brooklyn

**Chief, Cardiology Division, Coney Island Hospital; Assistant Professor, Department of Medicine, State University of New York, Downstate Medical Center, Brooklyn

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ity. Generalized atrophy and reduced function of muscle mass and most vital organs decrease the need for blood flow.

Accurate determinations of the cardiac response to carefully graded exercise is of greater importance. Few such data are available because of difficulty in finding suitable subjects and the potential hazards of vigorous exercise in the elderly. When these studies have been performed, they have yielded conflicting results, ranging from age-related decreases to small increases in cardiac output. These discrepancies may be related to variability in the way that the patient handles the work. Poor motor coordination, for example, may force some elderly people to perform inefficiently and exert more effort, while others may avoid a full workload. An example of the latter effect can be seen in treadmill studies in which patients learn to avoid muscular activity and factitiously appear to increase their exercise tolerance. If one attempts to define workload by maximal heart rate achieved, other difficulties arise. Cardiac pacemakers and conducting fibers also deteriorate with age at a variable pace so that heart rate is not solely a function of work.

Because of these experimental difficulties, it is necessary to approach the problem through indirect parameters of cardiac function that are less influenced by non-myocardial factors. A useful non-invasive method of studying cardiac function is the measurement of the systolic time intervals. With simultaneous recording of electrocardiographic, phonocardiographic, and carotid pulse tracings at high speed, one can determine the relative duration of each portion of the cardiac cycle (Fig. 1). The interval from the Q wave to the onset of the carotid pulse represents the pre-ejection period (PEP) and can be further divided into the first period (Q wave to first heart sound) and second period (first heart sound to onset of pulse). The ejection period (ET) corresponds to the interval between the onset of the carotid pulse and its dicrotic notch. As an alternate to the first heart sound, the apex cardiogram can be used to time the beginning of left ventricular contraction. In the absence of valvular disease, the ratio of ET to PEP rather closely reflects left ventricular contractility. Several studies have demonstrated an age-related decrease in ET and an increase in PEP. The former results from a diminishing stroke volume, and the latter reflects the speed with which the left ventricular wall generates its contractile force. This prolongation of the contractile process is probably caused by changes in visco-elastic properties and slower calcium delivery to and/or removal from contractile proteins.

The fall in stroke volume and slower contractility result in a rate-dependent cardiac output. The range of optimal heart rate narrows, and mild tachycardia or bradycardia may lead to significant deficit in blood flow to vital organs.

In short, the physiologic changes in the aging heart are such that it maintains its ability to function with an adequate output under normal conditions. However, the heart may not be able to respond normally to such stressful situations as blood loss, excess parenteral infusions, hyperthyroidism, or tachycardia. Under these circumstances, congestive heart failure, arrhythmia, or myocardial ischemia may ensue.

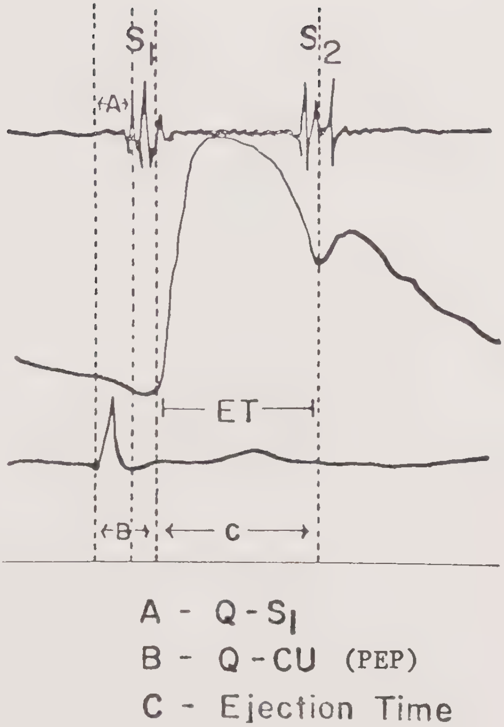

Figure 1. Simultaneous recording of electrocardiogram, phonocardiogram, and carotid pulse demonstrates the systolic time intervals. (*From* Friedman, S., and Davison, E. T.: Amer. Heart J., 78:752-756, 1969, reproduced with permission.)

The electrocardiogram shows no specific changes with age, but the prevalence of abnormalities in even asymptomatic individuals rises steeply in the seventh decade. An electrocardiographic survey[34] of 396 patients over age 74 revealed a normal electrocardiogram in 38 per cent (Table 1). There is a tendency for the electrical axis to shift toward the left with aging.

X-ray interpretation may be hampered by chest deformities caused by kyphoscoliosis and emphysema which may alter the relation between the chest and the heart and increase or decrease the transverse diameter of the thorax. In a radiographic survey[30] of 120 consecutive patients aged 65 years and older, the mean diameter of the heart when patients with increased cardiothoracic ratios were excluded was 13.2 cm for men, and 12.2 cm for women, not significantly different from the authors' young control group. When the cardiothoracic ratio exceeded 50 per cent, all patients but one exhibited significant clinical disease such as longstanding hypertension or organic heart disease. The aortic arch frequently shows calcification and tortuosity of the aorta and may have to be differentiated from aneurysmal dilation. Intracardiac calcifications may be due to calcified ventricular aneurysm; calcification of the mitral ring or the mitral or aortic valves; constrictive pericarditis or coronary artery calcifications.

There are several factors that make clinical diagnosis and assess-

Table 1. *Results of Electrocardiographic Survey of 396 Patients 75 Years of Age and Older*

CATEGORY	PER CENT
Normal electrocardiogram	38
Myocardial infarction (acute or residual)	7
Myocardial ischemia	7
Left bundle branch block	9
Right bundle branch block	10
Left ventricular hypertrophy	2
Atrial premature contractions	8
Ventricular premature contractions	5
Atrial tachyarrhythmia	17
Ventricular tachyarrhythmia	0
Digitalis effect	24
Atrioventricular heart block	5
Miscellaneous abnormalities	1

From Wasserburger, R. H.: Postgraduate Medicine, *58*:147, 1975, reproduced with permission.

ment of cardiac disease more difficult in elderly patients. Restricted physical activity diminishes the opportunity to experience the two cardinal symptoms of cardiac disease: dyspnea on exertion and chest pain. Many patients, for example, with both peripheral and coronary artery disease have relatively little angina because walking is limited by intermittent claudication. It is quite common to see an elderly patient with relatively asymptomatic left ventricular disease develop acute pulmonary edema after indiscreet use of salt during one meal or after an emotional upheaval. On the other hand, fatigability, weakness, lightheadedness or even focal neurologic symptoms may be early symptoms of low cardiac output.

Examination of an elderly patient in heart failure may reveal a surprisingly brisk upstroke of peripheral pulses and a wide pulse pressure because of loss of elasticity of the aorta and its major branches. The point of maximal impulse may be difficult to find even with significant left ventricular enlargement because of kyphoscoliosis or hyper-resonant lungs. Atrial gallop (S_4) is commonly heard in the elderly even in the absence of clinical heart disease as a result of decreased ventricular wall compliance.

Some elderly patients will manifest heart failure primarily as a cachectic state with marked muscular atrophy, weight loss, and anorexia. These findings together with a firm, palpable liver can lead to a mistaken diagnosis of cancer. Other patients may present with jaundice, ascites, and hepatosplenomegaly secondary to occult portal hypertension from longstanding right ventricular failure. In both cases, a wrong diagnosis can be avoided by listening for a protodiastolic gallop (S_3) and carefully examining the neck veins.

With this discussion as a background, let us now look at the clinical behavior in the aged of various cardiac abnormalities.

ISCHEMIC HEART DISEASE

Ischemic heart disease is the most important cardiovascular disorder of the elderly. Rodstein[31] reports that 72 per cent of cardiovascular deaths in the United States occur in those over 65 years of age. The Framingham Heart Study shows a marked increase of coronary artery disease and myocardial infarction with advancing age.

In almost all cases, the etiology of ischemic heart disease is caused by atherosclerosis of the coronary arteries although on occasion, embolism, aortic stenosis, or subaortic stenosis may cause myocardial ischemia. The atherosclerotic process remains asymptomatic for several decades in most subjects, and permanently so in many. During the fifth and subsequent decades, symptoms often appear because of luminal narrowing due to: (1) progression of the atheromatous process, (2) thrombosis, or less commonly (3) intramural hemorrhage, (4) vasoconstriction, or (5) a combination of these processes.[17] Atherosclerosis is a multifactorial disease. Diet, high in saturated fat and cholesterol, emotional stress, physical inactivity, hypertension, diabetes, smoking, and inherited factors, including hyperlipidemia, play a role in the development of atheromatous lesions. Some measures aimed at retardation of established atherosclerosis in the aged seem to have limited effectiveness, particularly when no underlying lipid defect is present. The Coronary Drug Project Group[33] showed that drugs such as clofibrate and niacin, used for secondary prevention of myocardial infarction because of their reported ability to lower cholesterol and triglyceride levels, did not prolong the patient's life during the study period of the project.

Angina pectoris in the elderly is more likely to have atypical features than in younger individuals. One frequent difference is the substitution of dyspnea on exertion for chest pain. This dyspnea is provoked by the same stimuli as ordinary angina and may be associated with a slight sense of chest tightness. It is distinguished from left ventricular failure by the absence of orthopnea and paroxysmal nocturnal dyspnea. Other patients have atypical distribution of pain that simulates other medical entities. For example, angina may be heralded by the onset of paroxysmal epigastric pain that may even appear to be relieved by antacids. When this pain occurs during the night, angina decubitus may be mistaken for ulcer pain. Frequent episodes after meals with radiation to the chest might lead to a diagnosis of hiatus hernia with peptic esophagitis. In some patients, angina manifested as recurrent left shoulder or wrist pain or tightness in the neck may be diagnosed as osteoarthritis. Finally, there are some patients who develop palpitation on exertion rather than pain either due to sinus tachycardia or an ectopic rhythm induced by cardiac ischemia.

In addition to taking a careful history, a clinician can obtain some clinical clues to the presence of angina by examining the patient during an attack. Angina is often associated with transient left ventricular failure, and a transient atrial gallop or paradoxical splitting of the second sound may be found. In some cases a murmur of papillary muscle dysfunction may appear. In most but not all cases, S-T segment or T-wave changes will be seen in the electrocardiogram. If a patient has recurrent angina pectoris and must take more than occasional sublingual nitroglycerin, a preventive regimen can be tried. This may consist of sublingual isosorbide dinitrate 5 mg, or nitroglycerin before activities known to cause angina. The more severe cases require beta-blockers, of which the best known in the United States is propranolol. Its pharmacologic action is mainly a decrease in myocardial contractility and heart rate which in turn diminish the oxygen consumption. One might start with 5 mg four times a day with increments of 5 mg until the symptoms are relieved or side effects appear. Amounts of over 160 mg daily should be given cautiously. In patients who have borderline evidence of heart failure, propranolol may be given with digitalis preparations.[9] The most common side effects of propranolol are bradycardia, hypotension, bronchospasm and aggravation of heart failure. When angina pectoris occurs frequently, is prolonged, or occurs at rest, hospitalization is generally indicated because the possibility of an impending infarct is great.

Acute myocardial infarction in the elderly may not have the same symptomatology as in the younger age group. The patient might present with shortness of breath secondary to acute left heart failure or may be seen in pulmonary edema without significant chest pain. At other times, a patient is seen with an acute cerebrovascular episode or syncope caused by hypotension, arrhythmia, or emboli due to myocardial infarction. As with angina, the radiation of the pain may be prominent, and may extend to the abdomen. Physical examination of the elderly does not differ greatly from the younger age group. A fourth heart sound is commonly heard, cardiac arrhythmias, signs of left heart failure, and hypotension are often found. The major complications of acute myocardial infarction are the same in younger patients and include: (1) cardiac arrhythmia, (2) pump failure occurring as cardiogenic shock or congestive heart failure, (3) systemic embolization, (4) ventricular aneurysm, (5) cardiac and interventricular septal rupture, (6) and papillary muscle dysfunction. When cardiac output is low, the elderly are more likely to show signs of mental confusion.

Several factors deserve attention when treating older people with myocardial infarction.[31]

1. Prolonged bedrest can lead to hypostatic pneumonia and phlebothrombosis. Passive and active exercises should be part of the daily routine and early mobilization must be weighed against the hazards of undue exertion.
2. The benefit of anticoagulation must be considered in the light of increased vascular fragility and susceptibility to intracerebral and intestinal bleeding. If warfarin is used, the prothrombin time should not exceed twice the control time.
3. Analgesia for chest pain should be achieved with small amounts of narcotics to prevent respiratory depression or aggravation of often coexisting bronchial disease.
4. A depressed mental state and agitation should be recognized as signs of cerebral anoxia and excessive sedation should be avoided.
5. Heart failure with congestion or pulmonary edema requires

diuretic therapy. Careful attention should be given to avoid dehydration and electrolyte depletion. Digitalis should be used cautiously in the elderly with damaged hearts as it may cause arrhythmias. Smaller amounts may be indicated.

6. The treatment of cardiogenic shock in all ages needs careful monitoring of pulmonary capillary or central venous and systemic pressure as well as urinary output. Intravascular fluid expansion has been shown to increase the preload and cardiac output in patients with low left atrial filling pressure, but because of the decreased myocardial reserve in the elderly, this approach is less well tolerated. Arrhythmia in the elderly with acute myocardial infarction should be treated promptly. Ventricular premature contractions should be treated with an intravenous bolus of lidocaine, 1 to 2 mg per kg, followed by an intravenous drip given at a rate of 1 to 4 mg per minute. Confusion, hallucination, or convulsions may be prominent side effects in the elderly. Ventricular tachycardia and fibrillation should be treated by immediate direct current shock.

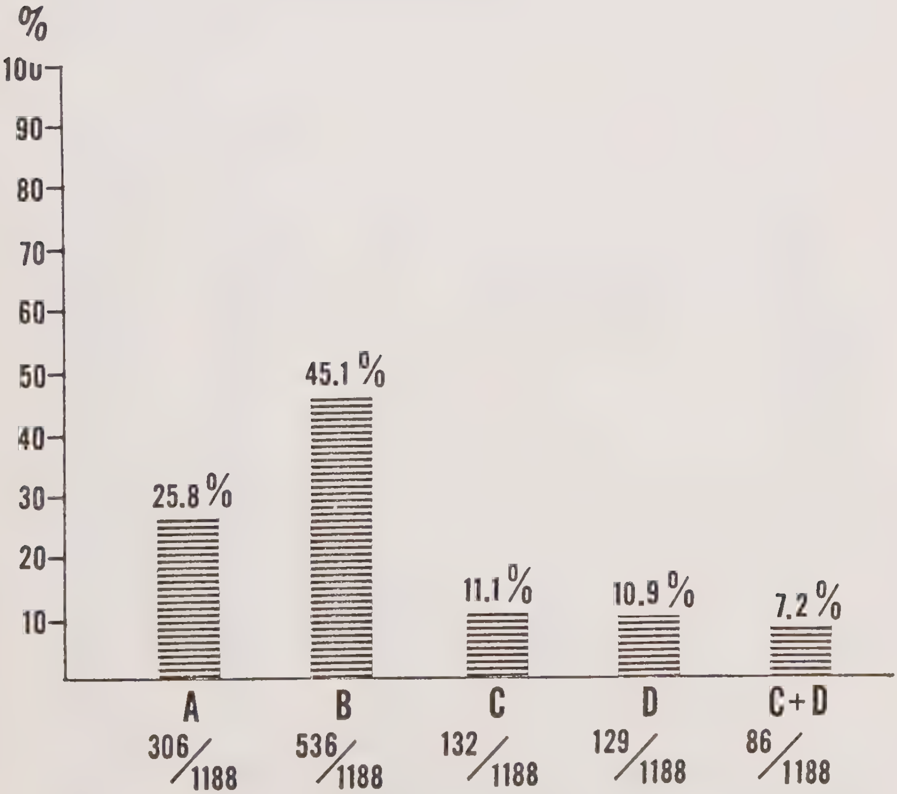

Figure 2. Classification of 1188 patients according to the severity of clinical status. *A*, No heart failure; *B*, heart failure; *C*, pulmonary edema; *D*, cardiogenic shock.

Atrial fibrillation with fast ventricular response can be managed by digitalization, unless associated with pulmonary edema or hypotension and requiring immediate control by cardioversion. The treatment of choice of atrial flutter is cardioversion. Sinus bradycardia with hypotension should be treated with small amounts of intravenous atropine. Caution should be exercised not to increase the heart rate excessively as this has been shown to increase the area of necrosis in experimental animals. There is no uniform agreement on the use of temporary pacing in patients developing bradyarrhythmias or heart block during acute myocardial infarction. In our opinion, a temporary transvenous pacemaker should be used for Mobitz Type II or higher degrees of block. Intravenous isoproterenol is the most effective means for temporary control of slow heart rate.

About 50 per cent of patients with acute myocardial infarction die before reaching a hospital, and 25 per cent of these patients have seen a physician 2 weeks prior to their death for symptoms of myocardial ischemia.[7] In myocardial infarction, Biorck[1] found a mortality of 33 per cent at age 60 to 69, 47 per cent at 70 to 79, and 64 per cent in those 80 years and over. In acute myocardial infarction[16] approximately equal sex distribution in the elderly has been noted by Biorck in contrast to the predominance of males in the younger groups. The University of Roches-

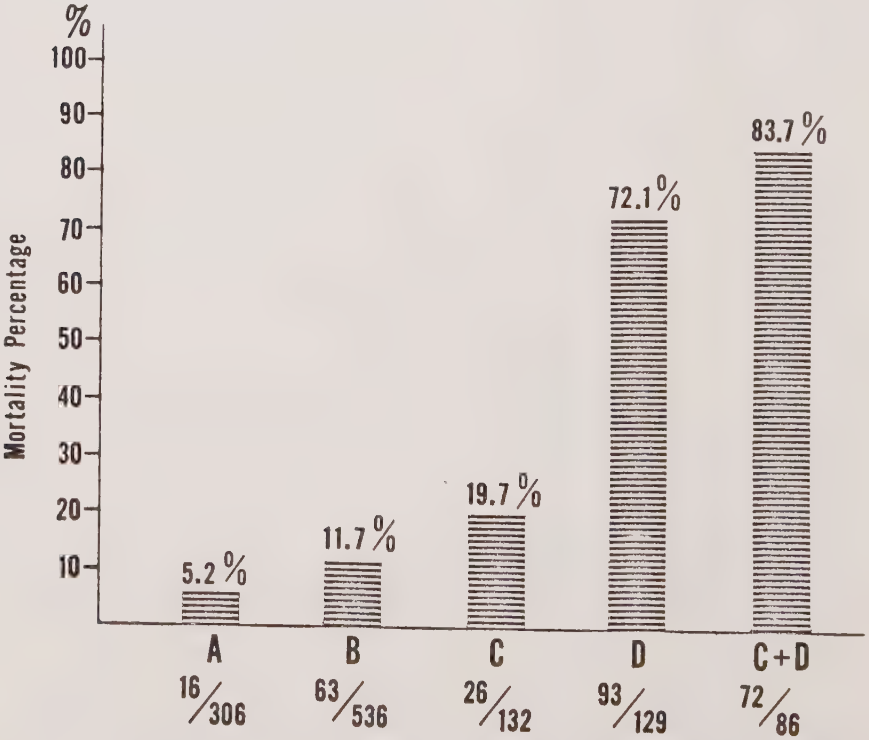

Figure 3. Hospital mortality according to the severity of clinical status in 1188 patients with acute myocardial infarction.

ter Group[24] has found that patients over the age of 65 have a significantly worse prognosis than younger patients.

Our own experience is derived from a review of factors in the prognosis of 1188 patients with acute myocardial infarction[20] admitted to the coronary care unit of Coney Island Hospital. The patients were classified according to the severity of clinical status (Fig. 2) and the mortality related to clinical status (Fig. 3). The total hospitalization mortality for 21 days or longer was 278 or 23.1 per cent. A history of hypertension and previous myocardial infarction did not significantly influence the mortality rate, but a significant association with diabetes mellitus was noted; 42/259 (31.6 per cent) who died had this disease. Of all the patients who died in the hospital (Fig. 4), 54.7 per cent died within the first 2 days, 72.7 per cent within five days and 94.2 per cent within 21 days. The mortality in patients with high degree of A-V block was 35.7 per cent. The results showed that patients with severe clinical symptoms, diabetes mellitus, and high degree A-V block had a higher mortality than the control group.

Cardiac surgery in coronary artery disease requires cardiac catheterization and selective coronary arteriography to determine if surgically approachable lesions are present. There is considerable disagreement about the advisability of the catheterization in the elderly,

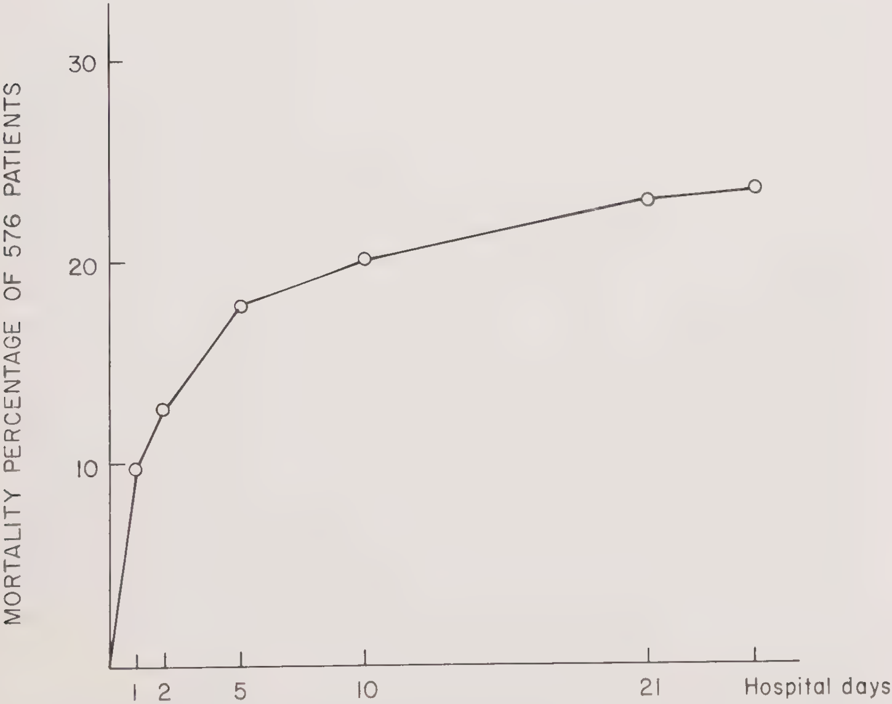

Figure 4. Mortality in patients with acute myocardial infarction related to a determined period of hospitalization.

but nevertheless catheterization is most commonly performed for the following conditions:

1. Intractable angina pectoris not responding to medical treatment.
2. Preinfarction angina not amenable to medical therapy.
3. For evaluation of ventricular aneurysm, interventricular septal defect and papillary muscle dysfunction which produce severe congestive heart failure.
4. Recurrent life-threatening arrhythmia not amenable to medical treatment.
5. Cardiogenic shock.[25,27]

A recent report on coronary artery bypass in patients over 70 years of age[26] revealed an operative mortality rate of 22 per cent. The overall mortality rate for all age groups was 6.4 per cent. These results strongly favor a conservative approach to coronary disease in the elderly. Two important indications for cardiac surgery in coronary artery disease are significant mitral insufficiency and a localized ventricular aneurysm. A double or wide, undulating apical impulse is suggestive of aneurysm, as are persistent S-T elevations on the electrocardiogram. The diagnosis is made by careful ventriculography. Although aneurysmectomy and/or mitral valve replacement carry a high surgical mortality, these procedures are justified in some patients with intractable heart failure.

VALVULAR HEART DISEASE

Mitral stenosis is almost always a result of rheumatic carditis and has been classically considered a disease of the young and middle-aged. Nevertheless, we see many elderly patients with this condition. The elderly patient with mitral stenosis usually has relatively mild valvular obstruction and becomes symptomatic either because of the development of other cardiac abnormalities or through arterial embolism. For example, a patient in the sixth or seventh decade with occult mitral stenosis may present for the first time with rapid atrial fibrillation and heart failure. Control of the ventricular rate with digoxin may eliminate his clinical problem. The amount of digoxin required bears no relationship to the severity of the stenosis.

It has been estimated that at least 20 per cent of all patients with mitral stenosis have at least one arterial embolus in a lifetime. In patients with mild and hemodynamically insignificant mitral stenosis, an embolus is often the first manifestation of the disease. In an elderly patient with atrial fibrillation and a stroke or transient ischemic episode, one must always look carefully for the auscultatory signs of mitral stenosis. In such a patient, a loud first heart sound should increase the index of suspicion. When there is a high degree of suspicion and a diastolic murmur cannot be heard, echocardiography may confirm the diagnosis. Further emboli can often be prevented with the use of anticoagulants.

The etiology of mitral regurgitation is more varied. In the elderly, mitral insufficiency is most often caused by papillary muscle dysfunction secondary to ischemic heart disease or myopathies, but may also be due to rheumatic carditis or bacterial endocarditis. Sometimes in papillary muscle dysfunction there is only a late ejection murmur rather than a holosystolic murmur.

Aortic valvular disease in the elderly is more frequently related to arteriosclerotic degeneration and calcification of the leaflets than to rheumatic carditis. These changes occur most often in the 2 per cent of the population with congenital bicuspid valves. Ejection systolic murmurs are common in elderly patients, and amyl nitrite testing usually indicates an aortic rather than a mitral origin. With the use of external carotid pulse tracings, approximately 40 per cent of aortic systolic murmurs of grade 2/6 or greater intensity have been found to be associated with significant stenosis. However, only a minority of these patients become symptomatic, perhaps because physical activity decreases with age. As in younger subjects clinical manifestations include angina pectoris, syncope and dizziness, and left heart failure. Angina and neurologic symptoms occur relatively more often in the elderly because of concomitant coronary and cerebrovascular disease. Clues to aortic stenosis, in addition to a murmur, include a decreased or absent aortic component of the second heart sound and slowly rising major pulses. It should be emphasized that a narrow pulse pressure is not necessary for the diagnosis of significant stenosis because pulse pressure tends to increase with age.

Systolic time intervals and carotid pulse tracings are useful in evaluating elderly patients with aortic systolic murmurs. In aortic stenosis, the latter demonstrates prolongation of upstroke or ejection time or both (Fig. 1).[35] The pre-ejection period (PEP) is frequently shorter than normal, and the PEP/LVET ratio is reduced in the majority of cases. Weissler suggests that left ventricular decompensation in aortic stenosis is associated with lengthening of the PEP and shortening of LVET (normalizing of the systolic time intervals). Treatment of the heart failure can restore the prolonged LVET and shortened PEP.

Surgery for aortic valve disease must be approached with caution in the elderly and should be considered only in the presence of intractable symptoms. Complete investigation is necessary including cardiac catheterization and selective coronary arteriography. Extensive coronary artery disease, myocardial failure, the presence of associated respiratory insufficiency and other associated diseases which may interfere with postsurgical recovery or may carry a diminished life expectancy for the patient must be weighed against the surgical benefit. In aortic stenosis, the electrocardiogram is helpful in deciding whether catheterization is indicated. A left ventricular strain pattern in the absence of hypertension points to aortic stenosis as the major lesion, while low voltage and Q waves indicate a strong component of coronary artery disease.

Aortic regurgitation in the elderly may be related to dilatation of the aortic valve ring, as a result of long-standing hypertension and arteriosclerosis. Often the decrescendo diastolic murmur varies in intensity with blood pressure and may become inaudible with a 30 to 40 mm Hg fall in systolic pressure. It has been estimated that an aortic regurgitation murmur can be heard under optimal conditions in 2 to 3 per cent of the normal population over age 65. Rarely is this form of regurgitation clinically significant.

Aneurysms of the ascending aorta, however, may cause hemodynamically significant aortic insufficiency and congestive failure. Over 80 per cent of these aneurysms are also related to arteriosclerosis. When an aortic diastolic murmur is heard for the first time in a patient with acute chest or back pain, one must always consider the possibility of aortic dissection and carefully examine the peripheral pulses and chest x-ray. A high index of suspicion requires confirmation by aortography followed by immediate institution of hypotensive therapy.

The distinction between valvular and aortic root aortic regurgitation can usually be made on clinical grounds. In valvular disease, the aortic component of the second sound is usually decreased, and the murmur is heard best at Erb's point. When aortic ring dilatation causes aortic insufficiency, A_2 is maintained and often loud, and the murmur is usually loudest at the aortic area and along the right sternal border. Of course, valvular aortic insufficiency due to rheumatic carditis, bacterial endocarditis, and calcific degeneration is also seen in the elderly.

CONGENITAL HEART DISEASE

The diagnosis of congenital heart disease in the elderly requires an awareness of its existence in this age group. Adult survival with congenital heart disease encompasses many common and uncommon defects.[28] In clinical practice, the most frequent congenital defects found are bicuspid aortic valve and atrial septal defect (ostium secundum). Patients with atrial septal defect often remain asymptomatic until past the age of 40 or 50, when atrial fibrillation and atherosclerosis contribute to heart failure, causing fatigue, cough and dyspnea. In a study done by Markman,[23] almost 30 per cent of patients with atrial septal defect in the fifth and sixth decade were reported to have appreciable pulmonary hypertension. The auscultatory findings in atrial septal defect reveal a systolic ejection murmur at the left sternal border, and wide fixed splitting of the second heart sound. With a large left to right shunt, a diastolic murmur can be heard at the tricuspid area. Not uncommonly, the patients with atrial septal defect are carried with a diagnosis of mitral valve disease for a long time because the physical examination and chest x-ray reveal superficial similarities.

The electrocardiogram shows an rsr' in V_1 in a high percentage of cases. The chest x-ray in posteroanterior position shows a large pulmonary artery, full hilar shadows with pulmonary overvascularization, or the presence of pulmonary hypertension. A chest x-ray with barium swallow in the right anterior oblique position shows the absence of an enlarged left atrium. Cardiac catheterization shows a step-up of oxygen saturation in the right atrium, denoting a left to right shunt, and elevation of right ventricular and pulmonary artery pressures. Angiography may show associated partial anomalous pulmonic venous return. Cardiac surgery is indicated in symptomatic patients with hemodynamically significant shunts leading to pulmonary plethora or hypertension. The surgical results are excellent and surgical mortality is low.

CARDIOMYOPATHIES

The classification of cardiomyopathies by Goodwin and Oakley is the most widely accepted: 1. *Congestive*, due to poor systolic function. 2. *Hypertrophic*, with impaired diastolic compliance. 3. *Obliterative*, secondary to obliteration of ventricular cavities, e.g., amyloid, leukemia, periarteritis, endomyocardial fibrosis, Loeffler's syndrome. The causes of congestive cardiomyopathies in elderly patients are mainly viral infections or alcoholism. The clinical picture shows marked cardiomegaly, low cardiac output, and biventricular heart failure with a diastolic gallop. Systemic embolization and cardiac arrhythmias are common. Diagnosis requires exclusion of hypertensive, coronary, toxic and metabolic myopathies and restrictive pericarditis.

Hypertrophic (obstructive) cardiomyopathy has been described by Braunwald in 1960 as idiopathic hypertrophic subaortic stenosis (IHSS) and more recently by Epstein as asymmetric septal hypertrophy (ASH). In this myopathy, the cavity of the left ventricle is normal in diastole, but is reduced in systole, owing to encroachment by the hypertrophic septum and mitral valve apparatus. The common symptoms of asymmetric septal hypertrophy are fatigue, dyspnea, angina, and syncope on effort; nocturnal dyspnea and palpitations may also occur. Physical examination may reveal a fast rising pulse, a fourth heart sound, a systolic murmur at the left sternal border and apex, a double precordial thrust, and a reduced pulse pressure in post extrasystolic beats. The elctrocardiogram shows left atrial and left ventricular hypertrophy and infarction patterns. Since introduction of echocardiography, the diagnosis has been made more frequently. Goodin and co-workers[15] reported 6 patients with asymmetric septal hypertrophy in the older age group. Digitalis, diuretics, and nitrates had worsened the symptoms in 4 of 5 patients. The therapy of choice is beta-blockade.

AMYLOIDOSIS OF THE HEART

Amyloid infiltration of the heart is extremely common in the later decades, but its etiology is not known. Pomerance[29] found an incidence of amyloidosis of 10 per cent in patients dying over the age of 80 years and 50 per cent over the age of 90 years. The high percentage of amyloid found on the necropsy table is often seen in patients with nonspecific clinical findings in whom the diagnosis was not suspected ante mortem.

Exertional dyspnea, although the most common symptom, may be absent because of involvement of both ventricles. In these cases, patients may show evidence of right heart failure without significant antecedent left heart failure. Palpitation and syncope, secondary to arrhythmia, are less common, but may be the presenting symptoms. Heart murmurs are mostly absent but may occur with infiltration of the papillary muscles or mitral valve. The electrocardiographic findings are nonspecific and may show low voltage complexes, pathologic Q waves, intraventricular conduction delay and heart block. Hemodynamic studies show a picture which correlates with variable degrees of restricted ventricular filling, and a low pulse pressure, secondary to diminished myocardial contraction is often present. Because of absence of specific findings, the diagnosis of cardiac amyloidosis may be very difficult. A gradual onset of heart failure in the absence of chest pains and signs of involvement of other organs favors the diagnosis. In symptomatic patients, the heart failure is refractory to treatment, and the course is progressively downhill. the patients respond poorly to digitalis, and signs of toxicity on sub-optimal doses may be an early clue to diagnosis.

PERICARDITIS

Acute pericarditis due to viral infections is less common in the elderly group. In clinical practice, a pericardial friction rub is most commonly heard in acute myocardial infarction, post myocardial infarction syndrome, and uremia. Pericardial effusion in the elderly is most often secondary to neoplastic disease, especially bronchogenic carcinoma and breast cancer. Hypothyroidism may also lead to effusion. Tuberculous pericarditis can manifest itself as a febrile illness or shortness of breath due to pericardial effusion and cardiac compression. The acute phase may be overlooked in 50 per cent of cases, and the patient may first be seen with constrictive pericarditis.

Constrictive pericarditis, when fully developed, presents a picture of venous congestion, mild cyanosis, hepatomegaly, and ascites out of proportion to peripheral edema. Pulsus paradoxus may be present in the absence of cardiac enlargement. Pericardial calcification on the chest x-ray is often a helpful clue to the diagnosis.

THE HEART IN THYROID DISORDERS

Hypothyroidism

Elderly patients with undiagnosed hypothyroidism are occasionally referred because of the cardiovascular changes related to myxedema. Pathologic findings include mucoid infiltration of the myocardial fibers, interstitial edema, pericardial effusion, and accelerated coronary atherosclerosis due to hypercholesterolemia. Clinical abnormalities are bradycardia, angina pectoris, cardiac enlargement on chest x-ray, and occasional diastolic hypertension. Oxygen consumption, cardiac output, and peripheral flow are diminished. The circulation time is prolonged. In contradistinction to patients with heart failure, the cardiac output increases with exercise.

Pericardial effusions can be diagnosed by echocardiography and disappear after thyroid therapy has been established for several weeks or months. Cardiac tamponade is rare. Congestive heart failure occurs mostly in the presence of underlying heart disease. The electrocardiographic changes are bradycardia and low voltage of the complexes. The chest x-ray shows enlargement of the cardiac silhouette. An important laboratory finding is an elevated serum creatine phosphokinase (CPK) due to hypothyroid myopathy. In a patient admitted with chest pain, it could lead to an erroneous diagnosis of myocardial infarction. An elevated CPK with a plateau level of values would suggest hypothyroid myopathy.

In treating hypothyroidism, one must begin with a very small dose of replacement therapy (for example, ⅛ or ¼ grain of thyroid extract) and increase it very slowly over a few weeks or even months. Angina pectoris may be aggravated by full or too rapid thyroid replacement, and it may be necessary to leave the patient somewhat hypothyroid.

Hyperthyroidism

Hyperthyroidism influences the heart through hypermetabolism and sympathetic stimulation. The cardiac output is increased at rest and during exercise in patients without heart failure. The circulation time is shortened, but may normalize with heart failure or even increase. Although heart failure is rare in young thyrotoxic individuals, cardiac involvement may be the only obvious manifestation of hyperthyroidism in people over age 50.

The main manifestations of thyrotoxic heart disease are palpitation, shortness of breath, and fatigue. Cardiac examination reveals a hyperdynamic apical impulse and sinus tachycardia even during sleep. In some cases, a venous hum in the neck is a clue to the presence of a high output state. Paroxysmal or chronic atrial fibrillation is the characteristic arrhythmia of thyrotoxicosis although other forms of supraventricular rhythm disturbances occur. The frequency of arrhythmias increases with age and duration of the hyperthyroidism and underlying heart disease. Elderly patients with atrial fibrillation or congestive heart failure develop significant cardiomegaly. The pulse pressure is widened with slight elevation of the systolic pressure and slight lowering of the diastolic pressure. Electrocardiographic and radiologic findings are nonspecific. The treatment of the underlying thyroid disease will correct the cardiac manifestations. For the treatment of supraventricular tachycardia, beta-blockers are the drugs of choice. When congestive heart failure is present, digitalis, and diuretic therapy may be used along with propranolol.

COR PULMONALE

Pulmonary heart disease (cor pulmonale) is the term used for hypertrophy of the right ventricle, with or without congestive heart failure, resulting from diseases of the lungs or pulmonary vascular tree.[12] Acute cor pulmonale is almost always due to acute massive pulmonary embolism while the chronic form is usually secondary to chronic bronchopulmonary disease. In the elderly kyphoscoliosis, fibrosis, and emphysema are the major contributory factors to respiratory insufficiency. Cardiac failure is usually precipitated by respiratory infection and marked by aggravation of preexisting shortness of breath and the appearance of peripheral edema and liver enlargement.

The electrocardiogram may show sinus tachycardia, atrial arrhythmia, a tall P wave in II, III aVF and right axis of the P and QRS. The precordial leads show clockwise rotation with rS complexes. A tall R may be seen in V_1. In the presence of emphysema, low voltage is most marked in the extremity leads. X-ray of the chest shows evidence of underlying bronchopulmonary disease. Although the evidence of right ventricular hypertrophy is not always present, the main pulmonary artery and hilar shadows may be enlarged. When pulmonary hypertension is significant, the peripheral markings are reduced. Right heart failure is treated with diuretics and digitalis. These patients do not respond as well to digitalis therapy as patients with left heart failure, and digitalis toxicity is common.

CARDIAC ARRHYTHMIAS

Cardiac arrhythmias in the elderly are often occult, manifesting themselves by intermittent effects on other end organs. Dizziness, syncope, transient ischemic attacks and strokes may result from intermittent tachyarrhythmias or bradyarrhythmias that reduce perfusing pressure through stenotic cerebral arteries. Attacks of angina may be precipitated by tachyarrhythmias, which reduce diastolic filling time for the coronary arteries. If the arrhythmia is frequent enough, a chronic low cardiac output state may lead to aggravation of congestive failure or prerenal azotemia. It is imperative to monitor patients with continuous recording devices for at least 24 hours when syndromes suggestive of arrhythmia occur.

One of the most common causes of significant arrhythmia in elderly subjects with ischemic heart disease is the sick sinus syndrome (SSS). Its physiologic manifestations[11] include sinus bradycardia, sinus arrest, sinoatrial block with or without atrial or junctional escape rhythm, and atrial fibrillation. The patient's rhythm may exhibit periods of sinus bradycardia or junctional rhythm alternating with supraventricular or ventricular tachyarrhythmias. The clinical manifestations are dizziness, syncope, or palpitation with or without chest pain. The diagnosis of sick sinus syndromes must be based on electrocardiographic documentation. Vagotonia due to digoxin should be excluded. Sinus node recovery time after atrial stimulation may be delayed or there may be an absence of sinus rhythm after cardioversion. The treatment of sick sinus syndromes requires a permanent demand pacemaker for control of bradycardia; antiarrhythmic drugs may be needed for control of the tachycardia.

Ventricular premature contractions (VPC) have different clinical significance according to their location in the cardiac cycle and their frequency. Premature ventricular extrasystoles falling on the T wave of the preceding complex are more likely to be precursors of ventricular tachycardia than end-diastolic VPC's, as are two successive or multifocal VPC's. Because of the occurrence of ventricular tachycardia in asymptomatic patients with VPC's, Holter monitoring is useful. Hinkle[18] studied employed American men 60 to 65 years of age and found 16 per cent to have more than 10 VPC's per 1000 complexes and 2 per cent of men had more than 100 PVC's per 1000 complexes. Even in asymptomatic patients and subjects without known heart disease, there is an increased incidence of ventricular fibrillation and sudden death associated with premature ventricular contractions.

Ventricular tachycardia may be manifested clinically by syncopal episodes or palpitation or may go unnoticed. Once the diagnosis is established, the patient should receive lidocaine, 1 to 2 mg per kg intravenously followed by an intravenous drip. Procaine amide can also be used. In the absence of a prompt response, cardioversion by D.C. shock is indicated.

The various forms of chronic atrioventricular block are also more common in the aged. Although this condition is clinically associated with coronary artery disease, postmortem examination of the cardiac conducting system usually reveals nonspecific degeneration that is not well correlated with the degree and location of coronary atherosclerosis.

Second degree heart block is now better defined by His bundle electrogram, which permits localization of the conduction defect above or below the bundle of His. The defect in atrioventricular Wenckebach phenomenon is almost always above the His bundle. This type of heart block is seen after inferior wall myocardial infarction and digitalis toxicity. The ventricular rate is generally over 50 per minute and prognosis is good. In Mobitz type II, second degree heart block, the conduction defect is below the His bundle. The latter is frequently associated with an incomplete trifascicular block, is considered more serious and is much more likely to produce Stokes-Adams attacks and to necessitate implantation of a permanent pacemaker.[22]

Third degree heart block (complete) is diagnosed by complete independence of atrial and ventricular rhythms. When sinus rhythm is maintained, the atrial rate is normal, and the ventricular rate is dependent on the automaticity of the escape rhythm. A clue to the presence of intermittent complete atrioventricular block is the presence of bifascicular block (most commonly right bundle branch block with left axis deviation beyond —30 degrees) and trifascicular block (right bundle branch block, left axis deviation and prolongation of P-R interval in the absence of digitalis intake). These findings in a patient complaining of dizziness or other intermittent central nervous system complaints are usually indications for permanent pacemakers.

Atrial fibrillation is a common arrhythmia in the aged and ordinarily does not significantly jeopardize cardiac output if the ventricular response is within the normal range. Most often the cause is coronary artery or hypertensive heart disease, but rapid ventricular rates should make one suspect the possible presence of occult mitral stenosis or hyperthyroidism. The cardioversion of chronic atrial fibrillation to sinus rhythm is usually not advisable in elderly subjects because the likelihood of return to atrial fibrillation is high, and each rhythm change predisposes the patient to systemic embolisation. Digitalis and the antiarrhythmic agents are useful in preventing paroxysmal episodes of atrial fibrillation.

A word is in order concerning the role of serum potassium levels in the genesis of arrhythmias. Potassium tends to slow cardiac pacemakers, and the elderly tend to be more sensitive to small shifts in potassium balance. A slight rise in serum potassium to the upper limits of normal, particularly if the patient is receiving digitalis, may lead to bradycardia, hypotension, azotemia, and mental confusion. The syndrome is completely treatable without pacemaker implantation by lowering serum potassium. Conversely, low serum potassium can predispose to a variety of tachycardias.

It is extremely important, therefore, to follow periodically the serum potassium level in patients taking digoxin and potassium-depleting diuretics. Although most of these patients require supplementary potassium to offset their losses, some do not lose much potassium because of kidney disease and/or reduced renal blood flow. The latter should not receive potassium supplementation.

CONGESTIVE HEART FAILURE

Management of congestive heart failure in the elderly must take into consideration physiologic changes in other organs. Partially because of decreased glomerular filtration rate, digitalis toxicity is more common, and a lower dose may be necessary. Diuretics must also be used judiciously. Marked hemoconcentration may lead to thromboembolism, and diminished blood volume to postural hypotension. In patients with underlying lung disease, dehydration may lead to inspissated secretions and respiratory embarrassment. Metabolic alkalosis due to potassium and chloride loss may initiate a reflex-mediated decrease in ventilatory drive.

There have been several advances in the pharmacologic management of previously intractable heart failure. The loop diuretics (furosemide and ethacrynic acid) can be given in progressively larger doses with careful attention to blood electrolytes. Occasionally patients will have significant diuresis only on daily doses equivalent to several hundred milligrams of furosemide. A recently described modality is the use of peripheral vasodilators such as nitroglycerin and sodium nitroprusside to reduce the afterload on the failing ventricle. Dramatic results have been obtained in selected cases, bedridden patients returning to a significant level of daily activity.

CONCLUSION

The elderly heart is generally a pump that functions well under ordinary circumstances but has lost much of its physiologic reserve. It is this factor coupled with the presence of atherosclerosis in the blood supply of other vital organs that leads to dramatic clinical manifestations when the normal homeostasis is upset.

The clinician must recognize these inter-relationships and be alert to possible cardiac causes for a wide variety of seemingly unrelated symptoms.

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Coney Island Hospital
2601 Ocean Parkway
Brooklyn, New York 11235

Common Manifestations of Degenerative Arterial Disease

*Sandor A. Friedman, M.D., F.A.C.P.**

Arteriosclerosis is exceedingly difficult to recognize in its early stages. This ubiquitous process begins in childhood and continues unabated at a variable pace, causing clinically recognized disease only when it is far advanced. An artery can be lined with intimal atheromas and still be patent; there is not a demonstrable fall in perfusing pressure until at least two thirds of the luminal diameter is occluded. Ischemic symptoms may often be avoided even after complete arterial occlusion if the process has been slow enough to allow time for adequate collateral circulation to develop.

Because it is the most important limiting factor in patient longevity, arteriosclerosis has been the subject of more intensive research than any other aspect of medical science, and yet it is still very poorly understood. In fact, it is not clear that all arteriosclerosis is the same. Certain risk factors such as hypertension, hyperlipidemia, cigarette smoking, diabetes mellitus, excessive weight gain, and perhaps lack of exercise are common to degenerative arterial disease at all sites, but their relative importance varies. For example, hypertension plays a more major role in cerebrovascular disease than it does in other areas.

This variability is illustrated, in some cases, by contiguous areas of the arterial tree. Patients with aorto-iliac occlusive disease tend to have a different clinical profile from those with femoro-popliteal disease.[7] Aorto-iliac disease usually becomes manifest in the late 40's or 50's in contrast to the 60's in the case of femoro-popliteal disease. Diabetes mellitus, hyperlipidemia and aneurysms of the abdominal aorta are more often associated with femoropopliteal than aorto-iliac disease.

Aneurysms of the aorta and peripheral arteries are also grouped under the umbrella of arteriosclerosis, but the entire pathological process is clearly different. The crucial changes of aneurysm formation are in the media of the vessel with destruction of smooth muscle and elastic elements and their replacement by fibrous tissue. In reality, an aneurysm is an exaggeration in a localized area of a normal aging process. It is this process of arterial stiffening that results in a more forceful pulse and wider pulse pressure in older people. While aneurysms are commonly associated with intimal atheromatosis, this statistical correlation may reflect the relation of both to aging. It is not rare to find patients with multiple aneurysms and little or no evidence of occlusive disease.

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*Chief of Medical Services and Chief of Peripheral Vascular Disease Division, Coney Island Hospital; Associate Professor of Medicine, State University of New York, Downstate Medical Center, Brooklyn, New York

A discussion of theories of pathogenesis of arteriosclerosis is beyond the scope of this article. The purpose of this report is to focus on some common clinical problems, emphasizing an approach to therapy in elderly patients.

ARTERIOSCLEROSIS OBLITERANS OF THE LOWER EXTREMITIES

In any discussion of peripheral arterial disease, it is important to distinguish between skin and muscle blood flow within the extremities. Muscle needs relatively little blood flow at rest, but normal walking increases its perfusion requirements 5 to 10-fold. The skin and subcutaneous tissue of the feet can survive with a mean blood flow as low as a few milliliters per 100 ml of tissue per minute. For this reason, an active patient with mild to moderate large vessel disease is likely to have symptoms when walking, while a relatively sedentary person will develop symptoms only with far-advanced disease. If small vessel disease distal to the calf muscles predominates, a patient may develop a severely ischemic foot, threatened by gangrene, without difficulty in walking.

The only specific symptom of peripheral arterial obstruction is intermittent claudication. It is the hallmark of skeletal muscle ischemia, but its pathogenesis is as obscure as angina pectoris, its counterpart in the coronary circulation. Claudication may be pain, discomfort, or a feeling of tiredness or tightness, occurring only during walking and promptly relieved by rest. It is never experienced while sitting or standing still. With femoro-popliteal disease, claudication occurs in the posterior calf, while in aorto-iliac disease, it may be localized to the buttocks and lower back. Treadmill studies have shown that patients with muscle ischemia have, under standardized conditions, relatively constant walking tolerance from day to day. Once that tolerance is reached, discomfort will generally force them to stop and rest for a few seconds or minutes. Those few patients who manage to continue despite claudication will eventually fall because their supporting muscles become too hypoxic to function.

In clinical practice, intermittent claudication is often incorrectly diagnosed as an explanation for leg pain. Elderly people, in particular, frequently complain of a variety of musculoskeletal symptoms that are unrelated to vascular disease. Nocturnal cramps, for example, increase in frequency with age and are especially common in women. Their etiology is not known. Patients with lumbosacral spine disease often have leg pain that increases with walking, but also occurs at rest. Osteoarthritis of the hips and knees may cause calf and thigh pain, but the joints are generally tender, and the pain is aggravated by standing as well as walking. Gait is of diagnostic aid when the story is not clear. Patients with claudication, in contrast to musculoskeletal and neurologic problems, walk normally until pain develops. They are not helped by crutches or canes.

Pain of diabetic peripheral neuropathy can occasionally be difficult to distinguish from claudication since it often worsens with walking. Neuropathic pain is also present at rest and tends to occur in paroxysms. Since many patients with diabetic neuropathy also have arterial disease, it may be difficult to determine how much of the symptomatology is caused by each disease. Occasionally patients will be thought to have arterial disease because they tire when walking. In contrast to claudication, tiring is usually poorly localized and inconstant and occurs after the patient has walked relatively long distances. Patients with claudication can rarely walk more than 4 to 6 blocks.

Intermittent claudication is sometimes unrecognized because of incomplete or unclear history. Patients often claim to be able to walk for miles despite pain and fatigue, but they have forgotten the rest periods of traffic intersections. Other patients develop their symptoms so soon after commencing their walk that they do not recognize a relationship to walking. When this occurs with hip and buttock discomfort of aorto-iliac disease, claudication can easily be misdiagnosed as nerve root compression pain. Another variable is the surface used for walking. For example, a patient who cannot walk more than two blocks on city pavements may be able to walk half a mile on a springy surface such as a boardwalk.

The nonspecific symptoms of peripheral arterial disease are a function of cutaneous ischemia and consist of a sense of coldness, numbness and paresthesias, and rest pain of the foot. Coldness is difficult to evaluate because in most people it is due to vasoconstriction, and vasomotor tone varies greatly in the normal population. Unilateral coldness, recent onset of coldness, and coldness that persists after a good night's sleep under warm blankets are highly suggestive of arterial insufficiency.

Numbness and paresthesias may be caused by many disorders, and careful neurologic examination is needed to insure a proper diagnosis. In elderly people, paresthesias are more likely caused by diabetic neuropathy or lumbosacral spine disease than by ischemia. Other diagnoses not to be overlooked are combined system disease of pernicious anemia; spinal cord tumors, particularly metastases from breast, bronchogenic and renal carcinomas; and carcinomatous peripheral neuropathy associated with an occult neoplasm. Sometimes, patients with femoral artery obstruction complain of paresthesias or numbness of the toes only on walking. This phenomenon is probably caused by stealing of blood flow from the cutaneous circulation associated with marked vasodilatation of the arterioles perfusing the calf muscles.

Pain at rest, when it is caused by arterial insufficiency, is always a dire symptom. It corresponds to a total cutaneous blood flow capacity of less than 10 per cent of normal. This pain, due to ischemic neuritis, is characteristically burning and paresthetic in nature and confined to the foot. It is often aggravated by elevation above heart level and slightly improved by dependency. Although mild at first, it tends to progress and may become agonizing and unresponsive even to narcotic analgesics. A patient so afflicted may actually beg for amputation.

It is important to exclude other causes of foot pain before invoking a diagnosis of severe arterial insufficiency. Arthritis, infection, and other forms of neuropathy must be considered. Diabetic peripheral neuropathy can cause foot pain, but it is usually bilateral and symmetric. Local infection, particularly in a subungual area, can be difficult to recognize in a foot with well-established arterial insufficiency. There may be insufficient blood flow for inflammatory signs such as erythema, heat, and swelling, and the onset of severe pain may be mistakenly assumed to be a sign of worsening blood supply. If pain and tenderness are well localized, one must look carefully for fluctuation. Sometimes exploratory incision with a small, sterile needle is indicated.

Physical examination is more helpful in diagnosing and evaluating peripheral arterial disease than any other circulatory ailment. Most important is accurate pulse palpation and an appreciation of the limits of normality. While the dorsalis pedis pulse may be congenitally absent (usually bilaterally) in perhaps 5 per cent of the normal population, the posterior tibial pulse should always be present. In the absence of significant ankle edema or marked orthopedic deformities, the failure of a skilled examiner to find a posterior tibial pulse is evidence of arterial occlusive disease. Intermittent claudication is usually associated with weakening or absence of the femoral and/or popliteal pulses, but some patients may have claudication secondary to posterior tibial occlusion or rarely to small vessel disease. In the last mentioned situation, the pulses would be normal.

In some patients, particularly those with aorto-iliac occlusion, all pulses may feel normal to a careful observer even though significant stenosis is present. One is unlikely to notice obstruction unless there is a pressure gradient of at least 40 mm Hg, corresponding to an extremely stenotic vessel. However, a patient with a pressure gradient of 20 mm Hg may have a 33 per cent reduction in blood flow through the vessel at rest and an even greater one during exercise. This certainly can be associated with marked claudication (Fig. 1). It is essential, therefore, to measure systolic blood pressure in the limb of a patient with normal pulses and a history compatible with intermittent claudication. The blood pressure in the leg may appear 10 to 20 mm Hg higher than in the arm because of cuff artifact, but it should never be lower than arm pressure. Blood pressure can be measured with a wide thigh cuff by listening over the popliteal pulse or more easily by palpation of a pedal pulse with the cuff just above the ankle. If arm and leg pressures are approximately equal in the supine position, the leg should be exercised, preferably until symptoms begin. Distal to an arterial obstruction, blood pressure falls during exercise, and the magnitude of the decrease and its duration after cessation of movement are proportional to the degree of arterial insufficiency. Blood pressure may fall sufficiently for pedal pulses to disap-

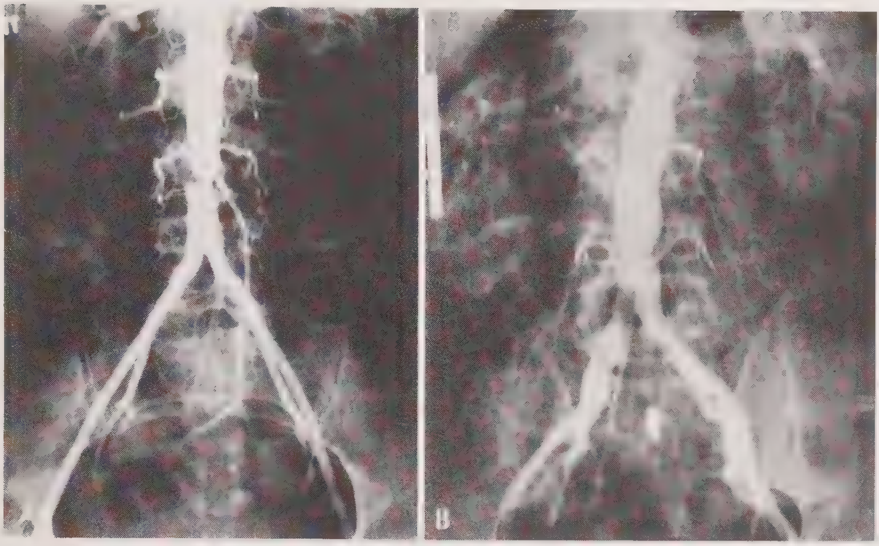

Figure 1. Aortograms of two patients with intermittent claudication and normal peripheral pulses. *A*, Aortogram demonstrates stenosis of the distal aorta. *B*, Aortogram shows stenosis of the right common iliac and left external iliac arteries. (*From* Friedman, S. A. et al.: New Eng. J. Med., *271*:1382, 1964, reproduced with permission.)

pear. In the past, many patients with aorto-iliac disease, normal pulses, and an unclear history have been misdiagnosed because these simple maneuvers were not performed. A femoral artery bruit is another sign of aorto-iliac disease. Short bruits may not be indicative of significant obstruction, but long bruits, especially if associated with a thrill, signify marked occlusion. Exercise, by increasing blood flow, is helpful in producing a bruit that might otherwise be obscure or inaudible.

The other signs of arterial disease are related to decreases in cutaneous blood flow and may not be present if collateral circulation is adequate. The foot or toes may be slightly cooler on one side than the other. With experience, one can detect by palpation a difference of one degree. The foot should be elevated above heart level for at least 20 seconds in order to ascertain whether there is blanching of the skin and then placed below heart level to watch for return of color and for filling of peripheral veins. In a normal subject, there will be little or no blanching on elevation, and dorsal foot veins will fill within 10 to 15 seconds on dependency. In the presence of varicose veins, venous filling time is of no diagnostic value because of retrograde flow.

If blanching on elevation is present, one should keep the foot dependent for at least 2 minutes, looking for the slow development of a homogeneous, violaceous rubor. This rubor is most marked distally and in extreme cases may be intensely cyanotic and apparent even with the foot at heart level. The discoloration probably represents unoxygenated blood pooling in capillaries dilated because of hypoxia. It is associated with a poor prognosis. Hypoxia may also lead to increased capillary permeability and the appearance of petechiae.

Sometimes there are localized areas of cyanosis or gangrene on the foot or toes, indicating small vessel disease. This small vessel syndrome, especially if distal pulses are present, should alert the clinician to the possible presence of several conditions including thrombocytosis, dysproteinemias, popliteal artery aneurysm, and collagen-vascular diseases.

Gangrene and ischemic ulcers are the ultimate sequelae of severe cutaneous ischemia. The first stage of gangrene is ecchymosis, which is distinguishable from cyanosis by its blanchability. Ischemic ulcers tend to be pale, often surrounded by a cyanotic border and are usually located on the heel, on a toe, or at the lateral malleolus.

Once a diagnosis of arterial insufficiency is made, therapy must be planned. Patients can be usefully divided into three broad categories: an asymptomatic group, those whose only symptom is intermittent claudication, and those with foot ischemia. The majority of patients with peripheral arterial disease are asymptomatic with relatively good collateral circulation and are detected only by careful palpation of pulses. Elderly people are often asymptomatic even with far advanced disease because they may not walk sufficient distances to experience claudication. Certainly screening for arterial occlusive disease is a cardinal requirement in the practice of geriatric preventive medicine. Most asymptomatic patients will not have enough progression of the basic arteriopathy to endanger the limb unless some form of trauma occurs. Trauma, whether thermal or direct, increases local tissue metabolism to a point where it outstrips a previously adequate blood supply and results in gangrene.

Those patients found to have asymptomatic disease should be given careful instructions concerning proper foot care:

1. Avoid temperature extremes. Direct heat may burn the foot, and coldness causes vasoconstriction.
2. Carefully cut toe nails straight across but not too short. They are preferably handled by a podiatrist.
3. Avoid trauma, and do not walk bare-footed.
4. Wear comfortable shoes.
5. Inspect feet periodically. Any discoloration or break in the skin should be shown to a physician or a podiatrist.
6. Do not smoke. Nicotine is a vasoconstrictor, and tobacco accelerates arteriosclerosis.

In addition, diabetic patients with neuropathy may have impaired distal sensation and should be warned that a visible lesion may be dangerous even if it causes no pain.

There is no effective medical therapy for intermittent claudication. The excessively advertised vasodilating drugs are of little help because they do not increase muscle blood flow sufficiently to meet the demands of normal walking. Only one modality is useful: arterial bypass surgery. Many factors must be taken into consideration in deciding which patients with claudication as their only complaint are candidates for surgery. Since claudication is not a threat to limb survival, one must assess the patient's need for prolonged walking, the degree of his disability and associated arteriosclerosis at other sites. A patient with significant angina and three-block claudication may derive little or no benefit from a successful revascularization procedure if his walking is still severely limited. Furthermore, risks of surgery are certainly significantly increased by the presence of active coronary or cerebrovascular disease. A patient who must walk long distances quickly to earn a livelihood must be considered differently from one who leads a more sedentary existence. Finally one must temper enthusiasm for surgery with the knowledge that an unsuccessful procedure sometimes leaves a limb more ischemic than it was before because collateral vessels have been sacrificed.

When one takes all factors into account, it becomes obvious that a very conservative approach toward arterial surgery is appropriate in elderly patients. Furthermore, they often have bilateral femoro-popliteal disease necessitating two procedures for relief of claudication. Walking to the point of pain should be encouraged because this tends to stimulate development of collateral circulation. Some patients notice marked improvement or even complete relief from claudication within several months of its onset. Therefore, no patient should be submitted to surgery for intermittent claudication until it has been present for 4 to 6 months.

Patients with cutaneous ischemia must also be individually evaluated. Rest pain, marked dependent rubor, and extensive skin breakdown are indications for surgical intervention. Localized areas of ischemic ulceration or gangrene can often be treated medically. A small area of dry gangrene is not a major threat and should be allowed to demarcate and eventually be sloughed. Chances for healing are much better with autoamputation than surgical intervention in an ischemic field.

The treatment of ischemic ulcers requires meticulous attention to detail. Often survival of a limb depends on the judicious compulsiveness of the patient and his physician. The first step is to remove any cause of chronic trauma such as an ill-fitting shoe that may have led to ulceration. It is important to keep the ulcer free of pressure. This often requires soft pads and positioning of the foot so that the involved area does not touch the floor or mattress. A preventable heel ulcer, for example, often occurs in elderly, arteriosclerotic individuals when they are put to bed because the pressure on the skin of the heel is much greater than capillary pressure when the patient is in the supine position. Lukewarm soaks are useful whenever an ulcer is infected or has necrotic debris. Debriding agents such as collagenase and travase are helpful in the latter situation. Systemic antibiotics are of very limited use in infected lesions but are indicated if there is surrounding cellulitis. Local antibacterial agents are useful, and in our experience, a tri-iodide solution (saturated solution of potassium iodide and iodine) is the most efficacious. This agent is aplied as a "sandwich dressing" (a tri-iodide dressing between two dry gauze pads) so that it does not touch the wound directly. Iodine is liberated in controlled fashion into the ulcer.

In considering patients for arterial bypass surgery, high-quality arteriography with visualization of the arterial tree from distal aorta to the ankles is essential in order to evaluate run-off distal to the obstruction. This is the only indication for arteriography, which is not a benign procedure. Documentation of disease can be performed in a non-invasive manner with an oscillometer or Doppler flow meter. For successful by-pass surgery, a patent artery of adequate diameter is needed distal to the obstruction. Few patients with a strong popliteal pulse are suitable candidates because the major obstruction is usually in the tibial arteries where the vessels are often narrow. However, in recent years, it has become technically feasible in some of the patients to perform femoro-tibial by-passes with insertion of the distal anastamosis just above the ankle. In one series of 91 patients, the patency rate was 51 per cent after a 3 year period.[11] The final decision for or against any by-pass surgery is made after weighing clinical urgency and arteriographic appearance of the run-off.

Recently, two relatively low-risk procedures for treatment of aorto-iliac disease have become available: subcutaneous axillary-femoral[2] and crossover femoro-femoral shunts.[3] These operations are particularly suitable for elderly patients in whom laparotomy for aorto-femoral bypass may be quite hazardous. They can be performed mostly under local anesthesia and have facilitated salvage of seriously ischemic limbs in patients who could not have tolerated major surgery. Femoro-femoral shunts have a reported patency rate comparable to aorto-femoral by-passes (85 per cent after 3 to 5 years in one study[3]), but they can be performed only in patients with unilateral disease. These shunts may soon become the procedure of choice in elderly patients with unilateral iliac disease. Axillary-femoral shunts, subject to kinking and thrombosis, have a somewhat less favorable prognosis. The patient should be taught to palpate the graft pulse daily because thrombectomy of an occluded graft is often possible if performed promptly.

CEREBROVASCULAR DISEASE

The management of ischemic neurologic symptoms remains one of the most perplexing and controversial problems in geriatric medicine. Patients may present with transient focal attacks, dizziness and vertigo, or organic brain syndrome. Although focal neurologic abnormalities generally indicate the presence of cerebrovascular disease, extravascular factors may be of major importance. Elderly people often have transient disturbances of cardiac rhythm with neurologic symptoms as the only sequelae. Therefore, all patients with transient ischemic attacks should be monitored carefully for 12 to 24 hours in an effort to discover preventable arrhythmias. Congestive heart failure, anemia, intermittent hypoglycemia, and dehydration may also produce focal central nervous system symptoms in the aged.

Dizziness in the elderly is often caused, at least in part, by orthostatic hypotension that is not apparent from the history. Blood pressure should be measured after the patient has been supine for at least 10 minutes and then repetitively for 5 minutes after the patient stands up. Antihypertensive medication, diabetic neuropathy, and brain stem disease are the most common causes.

After extravascular causes are ruled out, the clinician must determine whether transient ischemic attacks are caused predominantly by extracranial or intracranial arterial insufficiency. It is important to record blood pressure in both arms, to palpate both carotid and subclavian pulses and to listen for bruits in the carotid bifurcation and supraclavicular areas. Internal carotid artery disease is common in people over 50, and many elderly patients have systolic neck bruits. A bruit occupying most of systole and clearly distinguishable from a cardiac murmur almost always indicates a stenosis of more than 50 per cent in the internal carotid artery.[9] A thrill and extension into diastole are signs of severe stenosis, but significant stenosis or total occlusion may also be present without a bruit. The pathognomonic neurologic findings consist of ipsilateral blindness or scotoma and contralateral hemiparesis, but the more frequent presentation is like middle cerebral disease: contralateral hemiparesis and homonymous hemianopsia. Ischemic episodes generally result from microembolization of platelet-thrombi formed on an atheromatous plaque at or near the carotid bifurcation.

The high morbidity rate of surgery (4 per cent in the best centers) and prospective evidence that most patients develop transient ischemic attacks before infarction[12] justify a conservative approach in asymptomatic patients. If major ischemic attacks occur, four-vessel angiography is indicated. There is good evidence that carotid endarterectomy is better than conservative care in symptomatic unilateral carotid stenosis.[8] Surgery may be beneficial for bilateral stenosis but the risks are much greater. Surgery is not helpful for a total occlusion or in the presence of significant, persistent neurologic disease.

Some patients with distal, unapproachable internal carotid disease may be candidates for superficial temporal-middle cerebral anastamosis if the common and external carotid arteries are patent. This anastamosis is relatively safe to perform and usually remains patent for a prolonged period, but therapeutic benefit has not been adequately documented yet.

The other surgically accessible extracranial lesions are in the subclavian system. In the subclavian steal syndrome, there is significant retrograde flow (up to 20 per cent of total cerebral blood flow) from the basilar artery through a vertebral artery into the distal subclavian artery.[5] This occurs on the side of a subclavian artery obstruction (usually on the left side) proximal to the origin of its vertebral artery as a result of a low pressure in the distal subclavian. Patients with the steal phenomenon have symptoms of basilar artery insufficiency such as dizziness, dysarthria, and diplopia, and these findings may be provoked by exercising the involved arm. Brain stem infarction is rare, but symptoms may be disabling enough to warrant surgical intervention.

The steal syndrome can be suspected when arm pressures are unequal and a weak subclavian pulse or subclavian bruit is found. To confirm the diagnosis, it is necessary to demonstrate arteriographically retrograde flow through the vertebral into the distal subclavian artery (Fig. 2). The surgical approach of choice is a shunting operation such as a carotid-subclavian or crossover axillary-axillary shunt. A carotid-

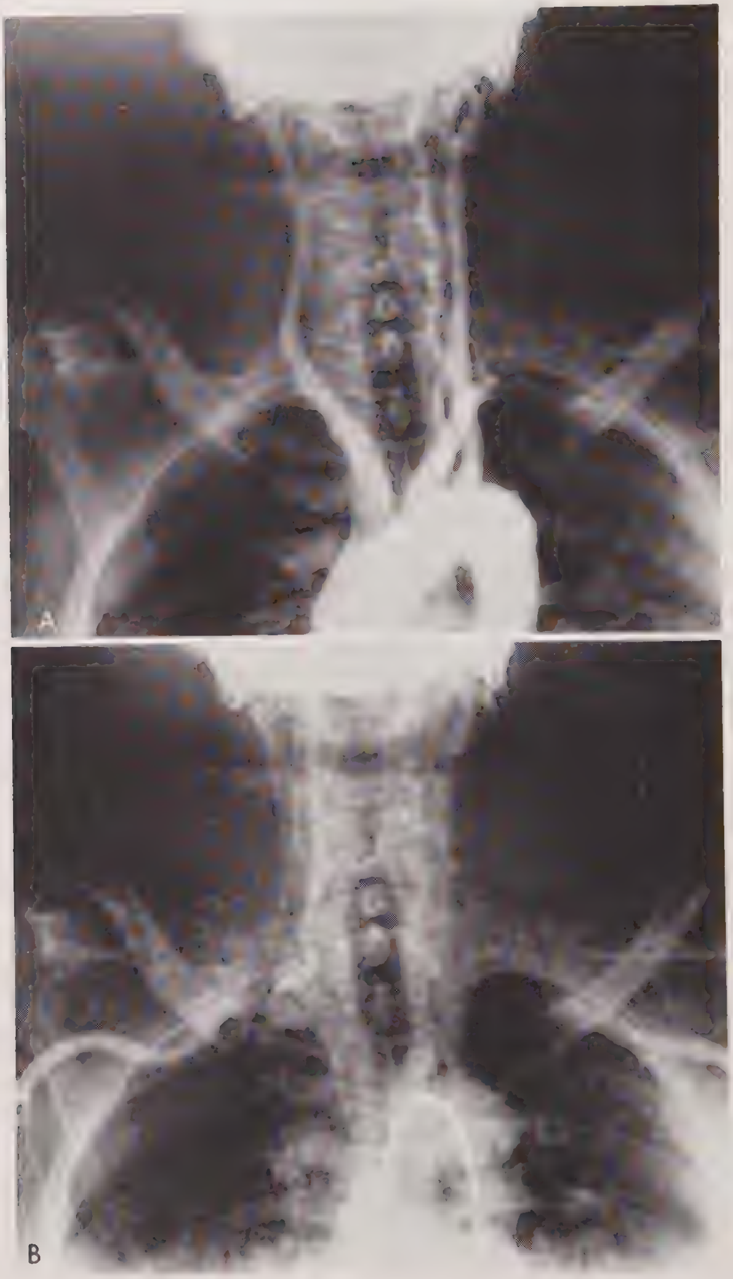

Figure 2. Aortic arch study of a patient with subclavian steal syndrome. *A*, Early film reveals occlusion of the right subclavian artery and normal filling of the left vertebral artery. *B*, Late film shows retrograde filling of the right vertebral and right subclavian arteries.

subclavian bypass is also feasible in an occasional patient with basilar artery insufficiency associated with unilateral, proximal subclavian obstruction, and a rudimentary vertebral artery on the other side.

There is little established therapy for patients with intracranial cerebrovascular disease. Chronic anticoagulation is controversial, some studies suggesting a decreased frequency of transient attacks, but none demonstrating an unequivocally lower incidence of strokes. Recently, interest has focused on use of antiplatelet drugs such as aspirin and dipyridamole as a means of preventing microemboli. There is some preliminary evidence that aspirin therapy can decrease the frequency of transient ischemic attacks.

ANEURYSMS

The frequency of aneurysmal dilatation is illustrated by a necropsy study of 7642 consecutive patients that revealed the presence of 249 aneurysms of the aorta or its major branches (3.3 per cent).[6] This figure did not include peripheral aneurysms. The abdominal aorta is the most common site, and multiple aneurysms are common. More than 50 per cent of patients with a popliteal aneurysm have or develop one in the other leg, and 35 per cent have abdominal aortic aneurysms.

The abdominal aortic aneurysm represents an important public health challenge in the middle-aged and elderly population since it is easily diagnosable, readily reparable, and highly lethal when left alone. For this reason, routine palpation of the abdominal aortic pulse is extremely important in patients past 55. When an aneurysm is present, this pulsation becomes expansile and is associated with a hard, globular mass. At times it is difficult to distinguish between an aneurysm and generalized dilatation and tortuosity. A helpful sign is the presence of obvious pulsation between the umbilicus. About 50 per cent of aneurysms are associated with a systolic bruit.

Sonography is the most useful laboratory procedure for confirming the diagnosis and estimating aneurysmal size and location. In most cases, sufficient information is obtained from physical examination and plain roentgenography of the abdomen. In approximately two thirds of these aneurysms, there is enough calcification to allow good visualization on an anteroposterior or transtable lateral view taken with proper bone technique (Fig. 3). All but about 2 per cent of abdominal aneurysms are located completely below the renal arteries, and those above the renal arteries are usually palpable at the xyphoid area. When location is in question, aortography may be necessary.

The evidence favoring elective surgical repair in lesions below the renal arteries is compelling. Through retrospective analysis, it has been estimated that rupture of abdominal aortic aneurysms accounts for about one of every 250 deaths in people over age 50.[10] Premonitory symptoms are rare; abdominal or back pain usually begins at the point of rupture or shortly before. Reported 5 year survival rates of untreated patients vary from 14 to 37 per cent, and marked improvement in longev-

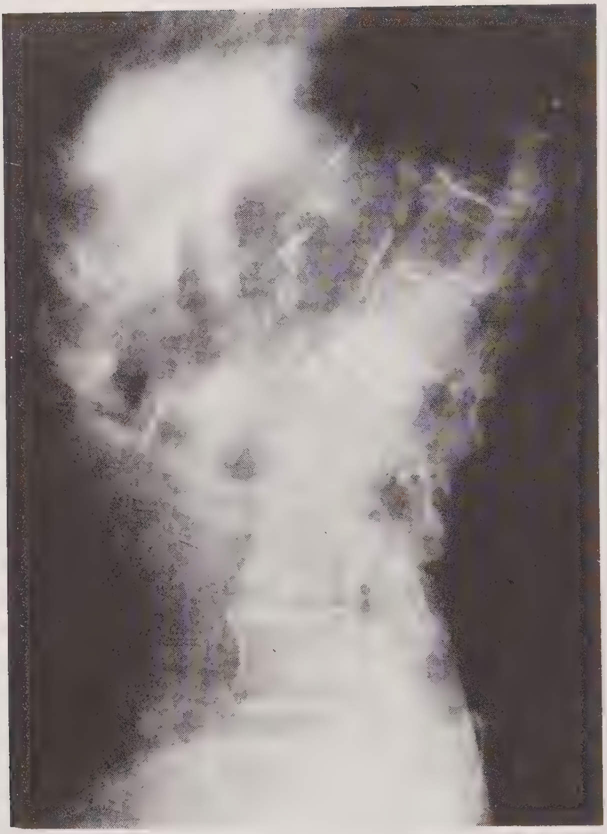

Figure 3. A lateral roentgenogram of the abdomen reveals the calcified posterior and anterior walls of a large aortic aneurysm.

ity after surgery has been demonstrated.[4] Surgical mortality in experienced centers is about 3 to 5 per cent. In one series with a 4 per cent mortality, the majority of patients had other cardiovascular disease including 46 per cent with coronary heart disease.[8] Advanced or unstable cardiac and cerebrovascular disease are the major contraindications.

Less frequent complications of aortic aneurysms are related to mural thrombosis within the dilated sac. Embolism to the lower extremities may be one explanation for the high incidence of femoro-popliteal occlusion in these patients. A few patients have even presented with consumption coagulopathy and purpura. Finally, extensive thrombi within the aneurysmal sac may serve as a nidus for infection, particularly in the course of salmonella septicemia.

The second most common aneurysm occurs in the popliteal artery because of compression in Hunter's canal, leading to post-stenotic dilatation. This lesion is easily diagnosed by careful pulse palpation. In some cases, the calcified borders can be outlined with a lateral roentgenogram of the knee (Fig. 4). Its major complications are thromboembolism, rup-

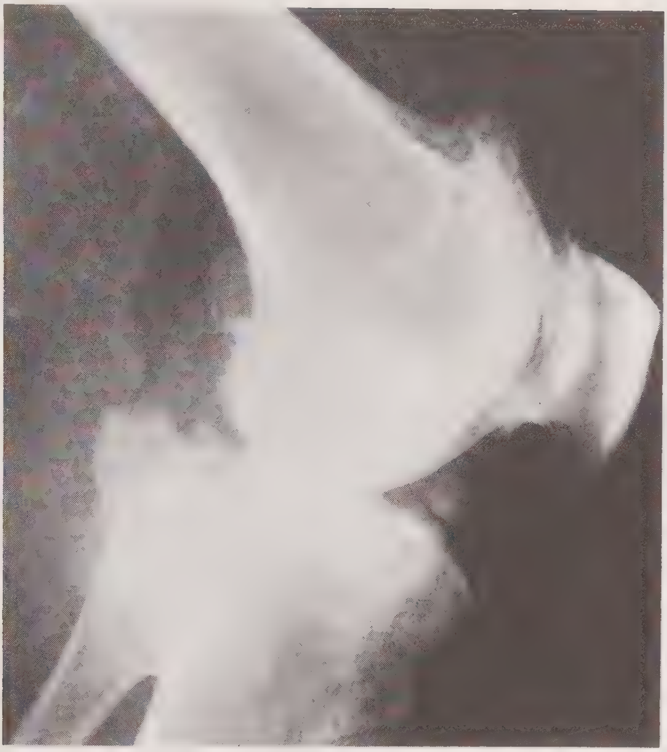

Figure 4. A lateral roentgenogram of the knee demonstrates a calcified popliteal aneurysm.

ture, and venous compression. Rupture occurs in approximately 10 per cent of patent lesions, but not in occluded aneurysms. Compression of the popliteal vein may result in edema and occasionally, venous thrombosis and pulmonary embolism. A few patients may complain of posterior calf paresthesias secondary to posterior tibial nerve compression.

The most common effects of popliteal aneurysms are caused by accumulation of mural thrombus, leading to chronic or acute popliteal artery obstruction or showers of distal emboli. Popliteal aneurysm should be the first diagnostic consideration in an elderly patient with repeated episodes of cyanosis of a foot or toe. The amputation rate in patients with popliteal aneurysms is high (11 per cent in one series), and surgical complication rates are extremely low.[13] Surgical repair, therefore, is indicated for almost all patent popliteal aneurysms. Treatment for occluded lesions is dictated by the severity of peripheral ischemia.

SUMMARY

The major focus of preventive medicine in the aged must be on the clinical consequences of peripheral arteriosclerosis rather than the disease process itself. Treating risk factors may be of some limited benefit. However, of most crucial importance is careful attention to premonitory symptoms and the state of the peripheral pulses including the abdominal aorta.

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Coney Island Hospital
2601 Ocean Parkway
Brooklyn, New York 11235

Venous Disease and Its Complications

Sandor A. Friedman, M.D., F.A.C.P.[*]

Venous thromboembolic disease and its sequelae account for a great deal of serious illness and death. It has long been known that pulmonary embolism is one of the most frequent causes of death in hospitalized patients. In one series of consecutive autopsies, histologic evidence of pulmonary thromboembolism was found in over 60 per cent of the patients.[4] Workmen's Compensation and other insurance records indicate that complications of chronic venous insufficiency are major causes of long-term disability and job absenteeism.

Until recently, few reliable data concerning venous disease have been available because of difficulties in diagnosis. New techniques have made objective diagnosis easier, and as a result, we have acquired much information in a few years. It is clear that the most significant factor in the development of venous thromboembolism is pooling of blood in peripheral veins, leading to stagnation and deposition of fibrin. Sedentary existence, bed rest, and congestive heart failure are important precipitating factors. Vigorous diuretic therapy to reverse cardiac failure often increases the likelihood of thrombosis by leading to hemoconcentration and increase in blood viscosity. Polycythemia, whether secondary to pulmonary disease or part of a myeloproliferative syndrome, acts in a similar manner. The increased prevalence of venous thrombosis in postoperative, postmyocardial infarction, and cancer patients may be related both to decreased activity and a possible hypercoagulable state. There is some evidence that surgery is associated with a decrease in the plasma concentration of activated factor X inhibitor. Since all these predisposing conditions increase in frequency with age, the elderly are at greatest risk for venous thromboembolism.

The most important physiologic characteristic of the venous system is the lack of an intrinsic propelling force. In an immobilized limb, unless it is raised above heart level, venous forward flow is completely abolished. Forward flow depends almost entirely upon the action of voluntary muscles in the extremities and the functional adequacy of a series of delicate, one way valves placed strategically throughout the

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[*] Chief of Medical Services and Chief of Peripheral Vascular Disease Division, Coney Island Hospital; Associate Professor of Medicine, State University of New York, Downstate Medical Center, Brooklyn, New York

venous system. These valves are easily damaged, and an incompetent valvular system quickly leads to aneurysmal dilatation of the relatively thin venous walls.

In the lower extremity where most venous disease occurs, one must distinguish between two interconnected venous circulations: deep and superficial. The deep venous system follows the major arteries and has the same nomenclature. The superficial system consists of the greater and lesser saphenous veins and their tributaries. The greater saphenous vein begins on the dorsum of the foot, traverses the medial calf and thigh, and empties into the femoral vein. The lesser saphenous vein begins on the lateral side of the foot and runs posteriorly through the calf to its termination in the popliteal vein. The deep system carries the bulk of venous flow under normal circumstances but can only be assessed indirectly. Visible venous prominence always represents the superficial (saphenous) system. With this background information, the pathophysiology of the major clinical disorders can be more easily understood.

DEEP VEIN THROMBOSIS

One of the most treacherous disorders in clinical medicine is thrombosis of a peripheral vein because it may remain totally occult until massive pulmonary embolism occurs. The percentage of cases that can be diagnosed clinically is small but varies with the skill and thoroughness of the clinician. The major prerequisite for the diagnosis of deep vein thrombosis of the lower extremities is rapid and sudden onset of unilateral edema over the course of hours or perhaps a day or two and most marked at the ankle. Although there is often obvious pitting edema, occasionally one will notice swelling only by carefully measuring the circumference of both legs near the ankles. Daily measurement of limb circumference in postoperative patients and patients at bedrest because of acute cardiopulmonary disease may reveal early evidence of venous thrombosis in some cases and allow for early therapeutic intervention.

Very few other entities cause sudden unilateral swelling of a limb. One must always exclude trauma. This is done by history and also by the nature of the swelling. Rupture of a plantaris tendon can resemble venous thrombosis in appearance, but the swelling is generally immediate, several inches above the ankle, and localized to the posterior calf. There is usually a history of sudden, violent dorsiflexion of the foot as when one steps abruptly into a hole. In ankle injuries, tenderness and swelling are confined to the ankle. A popliteal cyst may dissect into the fascia of the upper calf and simulate venous thrombosis, but this is distinguishable by the disproportionate swelling in the upper calf and relative sparing of the ankle area. In contrast to traumatic swelling, venous edema is often first noticed by the patient after a night's rest.

Pain, tenderness, and warmth may be present in venous thrombosis if there is sufficient inflammatory reaction. Pain and tenderness occur in the posterior calf in a popliteal-tibial thrombophlebitis and the medial thigh in ilio-femoral thrombophlebitis. It is important to emphasize that pain is generally mild and almost always is accompanied by swelling. Leg pain in the absence of obvious swelling is rarely due to thrombophlebitis.

Elderly patients, in particular, tend to have many nonspecific kinds of leg pain such as nocturnal cramps, pain of osteoarthritic joints, radicular pain from lumbosacral nerve compression, and peripheral neuropathy. Often no explanation can be found. In these situations, thrombophlebitis is often diagnosed as a last resort and therefore relatively dangerous therapy is frequently instituted. This is particularly true if the patient exhibits a Homan's sign (tenderness in the posterior calf on dorsiflexion of the foot). Unfortunately the latter has been accorded a great deal of specificity by many clinicians although it is entirely nonspecific. Any inflammatory lesion in the gastrocnemius sheath and even nerve root compression may be associated with this sign. Elderly people often exhibit a Homan's sign for no apparent reason.

Therapy for deep vein thrombosis remains anticoagulation. Although two experimental thrombolytic agents, streptokinase and urokinase, can actually lyse venous clots, there is still no evidence that fibrinolytic therapy results in lowered mortality or morbidity. The purpose of anticoagulation is to limit the propagation and extension of a venous clot. This has two important results: prevention of pulmonary embolism and preservation of as much venous valvular function as possible. The latter, although often not considered in planning of therapy, is important to prevent life-time morbidity secondary to chronic venous insufficiency.

Heparin is considered to be the most effective anticoagulant, but there is little agreement concerning mode of delivery or monitoring of dosage. The standard Lee-White clotting time is a rather unreproducible test even when performed under strict laboratory conditions, and many groups base heparin dosage on body size alone. There is preliminary evidence in heparinized patients of a direct relationship between activated partial thromboplastin time and likelihood of suffering a pulmonary embolism.[1] In several centers, heparin dosage is now regulated with this test. Heparin can be administered intermittently through either an intravenous or subcutaneous route or in a constant intravenous infusion. When administered subcutaneously, it is usually given every 6 hours and must be delivered in such a manner as to avoid fascial planes, preferably into the suprapubic fat pads. In elderly people in particular, the subcutaneous route may be uncomfortable and hazardous because hematomas often develop and may spread along tissue planes, leading to significant blood loss. Heparin is administered most commonly every 4 hours by the intermittent intravenous method. Recent work, however, suggests that continuous intravenous infusion, carefully controlled by a pre-set infusion pump, may be associated with the lowest incidence of hemorrhagic complications. In one study, evidence of significant hemorrhage was seven-fold higher in patients treated with intermittent doses than in those who received a continuous infusion of heparin.[11] In the latter, the activated partial thromboplastin time was maintained between 1½ and 2½ times normal. Further study of this method under close supervision seems warranted. There are no data to indicate any difference in efficacy among delivery routes.

The usual dose of heparin for treatment of deep vein thrombosis by the intermittent route varies between 5000 and 7500 units. The intensity of anticoagulation therapy is a matter of clinical judgment in each case. A patient with extensive ilio-femoral thrombosis obviously should receive more intensive therapy than one with tibial vein thrombosis. Age per se is not a contraindication to anticoagulation, but patients above the age of 60 are definitely more prone to hemorrhagic complications. In particular, one must be concerned about elderly women and elderly people with hypertension, who may be at risk of developing intracranial bleeding. Therefore, one is often justified in using sub-optimal doses of heparin in elderly patients with mild thrombophlebitis and a high risk of hemorrhage. If there is a definite contraindication to heparin such as active bleeding or several relative contraindications such as advanced age, mild hypertension, and a history of active peptic ulcer, one must consider interruption of the inferior vena cava as an alternative to anticoagulation. This modality will be discussed further in connection with pulmonary embolism.

In the past, it was customary to keep patients with deep vein thrombosis at bed rest for at least 10 to 14 days and to elevate the affected limb. There is no evidence that either of these measures is efficacious, and it is probable that both do more harm than good. Since thrombosis tends to occur when there is venous stagnation, movement of the limb is important, and the best way to accomplish this is to have the patient walking as soon as possible. The patient can usually be in a chair with the leg raised on the second or third day and can walk with elastic support on the third or fourth day. This is particularly important for elderly patients who tend to have less spontaneous movement while in bed. The leg should not be elevated above heart level unless the patient's upper trunk is flat; a "V" position significantly increases the risk of pulmonary embolism.

The proper duration of anticoagulant therapy is a matter of speculation. Our approach has been to base this decision on whether or not the original predisposing factor is still present. After an uncomplicated venous thrombosis associated with a self-limited illness, short term therapy is employed (usually 2 to 3 months). If risk of hemorrhage is high, therapy may be stopped after a few weeks. An elderly, immobile patient with chronic cardiac disease and a pulmonary embolus may be treated for a year or perhaps indefinitely, depending on his clinical course. It is customary to treat with heparin for the first 7 to 10 days and then continue with one of the warfarin derivatives. The patient should continue to receive heparin for at least the first 4 days of warfarin therapy even if the prothrombin time is in the therapeutic range sooner. It has been demonstrated that the only clotting factor adequately depressed in the first 2 to 3 days is factor VII, which is not involved in the intrinsic coagulation process. An alternative to warfarin is the use of low-dose subcutaneous heparin (approximately 5000 units every 8 to 12 hours).

Until recently the only accurate laboratory test for venous thrombosis was venography in which a radiopaque contrast substance must be injected into a dorsal foot vein. This is cumbersome and not suitable for mass screening. Introduction of two new techniques, impedance plethysmography and the radioiodinated fibrinogen test,[3] has revolutionized the diagnosis of asymptomatic deep vein thrombosis. The plethysmographic procedure capitalizes on the relatively high electrical conductance of blood. In a normal extremity, a venous tourniquet placed around the thigh will increase the venous blood volume and thereby decrease impedance to an electric current. If venous occlusion is already present, this change is dampened or absent.

The radioiodinated fibrinogen test entails the intravenous injection of human fibrinogen tagged with ^{125}I, an isotope with a relatively long half-life. This is the most sensitive test and gives very few false positive results. There is a slight risk of viral hepatitis unless the patient's own fibrinogen is used. After one injection, the legs can be scanned at the bedside for 10 to 14 days. Increased uptake indicates the presence of active venous clotting.

With these new procedures, it has been possible to show that clinical thrombophlebitis is the top of a huge iceberg. Studies on routine postoperative patients, for example, have shown incidences of occult venous thrombosis in the range of 21 to 34 per cent.[8,9] Frequencies as high as 46 per cent have been reported for certain high-risk procedures like hip-nailings. Similarly high incidences are found after myocardial infarction[6] and cerebrovascular accidents. The radioactive fibrinogen test has shown that most thrombosis begins in the soleal sinusoids and that the risk of pulmonary embolus is not high until the clot reaches the upper calf.[2] Thus a high-risk patient can be monitored and anticoagulated at the appropriate time.

An important revelation obtained from the radioactive fibrinogen test is the extremely effective prophylaxis against venous thrombosis afforded by low-dose heparin. This has been shown in postoperative and post-myocardial infarction patients. There is also evidence that low molecular weight dextran may be an effective prophylactic agent. Of even more importance are the results of a recent international study indicating a marked decrease in mortality due to pulmonary embolism in high-risk patients treated with low-dose heparin.[7] In a controlled trial of 4121 patients over the age of 40 who were undergoing major abdominal or thoracic procedures, 2046 received 5000 units of heparin subcutaneously 2 hours before surgery and at 8 hour intervals postoperatively for 7 days. The remaining patients did not receive prophylaxis. Autopsies were performed in 69 per cent of the 180 patients who died. Twenty-two pulmonary emboli (16 fatal ones) were found in the control group and only 5 emboli (2 fatal ones) in the treated group. Bleeding complications were minimal, and the treated patients did not require more transfusions than the controls. These results should encourage the use of low-dose heparin in high-risk situations, particularly in elderly people who tend to be less mobile.

The reason for the effectiveness of heparin in low doses is probably related to its effect on the clotting process before the formation of thrombin. Activated factor X is of critical importance in activating prothrombin, and heparin, even in small doses, promotes the action of the major plasma inhibitor of this factor.

The studies with radioiodinated fibrinogen have provided some other interesting findings. Elastic stockings and bandages, often routinely used in bedridden patients, appear to have little or no value in preventing venous thrombosis. However, measures designed to promote calf movement, such as periodic galvanic stimulation of the calf muscles intraoperatively and postoperatively, decrease the incidence of venous thrombosis significantly. Recently an inflatable boot that intermittently increases calf pressure to 40 mm Hg has been introduced as a means of simulating the normal skeletal muscle pump and preventing venous pooling. Initial results in surgical patients have been encouraging. These physical modalities are particularly well suited for elderly patients in whom anticoagulation is more hazardous and immobility during illness is more striking.

Special consideration should be given to ilio-femoral thrombophlebitis. It is not uncommon for this form of venous thrombosis to herald the presence of an occult neoplasm such as pancreatic carcinoma or to be caused by tumor invasion and compression of the iliac vein and/or inferior vena cava. The presence of either of two features especially in patients past 55 should alert the clinician to the strong possibility of cancer.

The first consideration is location. Most ilio-femoral thrombosis occurs on the left side because there is ordinarily mild compression of the left iliac vein by the left iliac artery as the former crosses the midline to join the inferior vena cava. Therefore, one must suspect the possible presence of an underlying coagulation disorder, collagen disease, or neoplasm when thrombosis occurs on the right side unless there has been obvious trauma to the right lower extremity. In an elderly person, cancer is the most likely of these diagnostic possibilities.

The second feature that is cause for similar concern is phlegmasia cerulea dolans, (ilio-femoral venous thrombosis associatcd with marked arteriospasm). In this entity, the foot and lower leg are cold, mottled and often pulseless. It is distinguished from acute arterial occlusion by the marked edema of calf and thigh. Since large clots are generally present in the common iliac vein and massive pulmonary embolism is an imminent threat, interruption of the inferior vena cava is advisable.

PULMONARY EMBOLISM

It is not the purpose of this article to summarize the massive literature concerning pulmonary embolism but rather to focus on those features most pertinent to the care of the aged. The development of radioactive lung scanning and pulmonary arteriography in the last decade has improved the accuracy of clinical diagnosis and has increased our knowledge of pulmonary embolism. Unfortunately most of the so-called "clinical pearls" described before the era of these diagnostic techniques are not reliable because they were based on diagnoses that were inconclusively established and often wrong.

The cardinal physiologic disturbance of pulmonary embolism is hypoxia, manifested by dyspnea out of proportion to physical findings.[12] This may be associated with evidence of acute cor pulmonale and right ventricular failure. If infarction occurs, pleuritic pain, hemoptysis, and hemorrhagic pleural effusion and/or lung consolidation develop. Infarction is present, however, in only a small minority of cases, generally when distal pulmonary arteries are occluded, or the patient has prior left ventricular failure.

Although these classical clinical patterns occur in patients of all ages, there are other common ways in which pulmonary embolism presents in the elderly. Acute pulmonary edema responding to the usual clinical measures is a frequent finding. It is rather surprising that a process causing pulmonary oligemia should lead to left ventricular failure, and the reason is not entirely clear. Most likely, pulmonary edema results from myocardial hypoxia in elderly patients who already have significant coronary artery disease. When recurrent episodes of pulmonary edema with no obvious precipitating event develop, pulmonary emboli should be suspected even in the presence of significant heart disease. Recognition of superimposed pulmonary emboli may result in the salvage of patients thought to have terminal left ventricular disease. Other patients may present with severe bronchospasm and be mistakenly treated for chronic obstructive lung disease. The distinction can often be made by the relatively normal mobility of the diaphragms and low plasma partial pressure of carbon dioxide in patients with pulmonary embolism and the greater difficulty in oxygenating them.

The distinction between pneumonia and pulmonary embolism becomes more difficult in the aged. Fever and leukocytosis are often blunted in the later decades, and a debilitated patient may have difficulty in coughing up secretions. The major clinical difference is the greater degree of hypoxia in pulmonary embolism.

There is no pathognomonic test for pulmonary embolism except pulmonary arteriography. Partial pressure of oxygen (Po_2) in blood and perfusion lung scanning, when normal, are useful in ruling out this diagnosis [13] but of little value in establishing it. This is particularly true in older people; the blood oxygen level decreases with age, and lung scans are often abnormal even in the absence of obvious cardiopulmonary disease.[5] However, disproportionately small increments in Po_2, despite use of high oxygen concentrations, should make one think of pulmonary embolism. Serial lung scans in association with a normal chest x-ray are useful in retrospective diagnosis since defects of pulmonary embolism should show evidence of gradual resolution within 2 weeks, whereas a defect due to chronic lung disease will persist. In most patients with pulmonary embolism, fibrin split products can be demonstrated in the plasma, but they may not be present at the onset of symptoms.

The indications for pulmonary arteriography vary with the experience and facility of each institution. In general the test is somewhat more hazardous in elderly people and we tend to perform it only when long-term anticoagulation or inferior vena cava ligation is contemplated. A clear delineation of the pulmonary vasculature requires catheterization of both main pulmonary arteries. Even then, in the presence of chronic lung disease, it may be difficult to differentiate intrinsic occlusion of segmental vessels from extrinsic compression secondary to interstitial fibrosis.

Scanning after inhalation of radioactive xenon (ventilatory scan) has been of diagnostic value in some cases. Since a pulmonary embolus without infarction leaves local ventilation undisturbed, the constellation of a normal ventilatory scan and abnormal perfusion scan is highly suggestive of pulmonary embolism. Unfortunately this test is often useless in the elderly because of the concomitant presence of ventilatory defects related to chronic lung disease and age-related reduction in pulmonary function.

Therapy for pulmonary embolism is basically the same as for venous thrombosis with the addition of adequate oxygenation and treatment of heart failure if present. One usually anticoagulates the patient for at least 2 to 3 months, and considerably longer if the original predisposing factors are still present.

Maintenance of a Po_2 of at least 50 mm Hg is important not only for protection of both the brain and myocardium but also to prevent pulmonary vasoconstriction. A vicious cycle of hypoxia and consequent pulmonary arteriolar vasoconstriction often aggravates the damage done by the original embolus.

The generally accepted indications for inferior vena cava interruption are: contraindications to anticoagulation, repeat pulmonary embolism despite adequate anticoagulation, massive pulmonary embolism, septic pulmonary emboli, and phlegmasia cerulea dolans.

Caval interruption can be achieved by surgery or through placement of an umbrella in the inferior vena cava. The umbrella is passed with a catheter through an internal jugular vein into the right atrium and down into the inferior vena cava and released under fluoroscopic guidance in the lower cava, where its prongs become lodged in the wall. Its final position should be just distal to the renal veins. The location of the latter can be estimated from an intravenous pyelogram, but more accurate placement via renal vein catheterization is preferable. If the umbrella is too far below the renal veins, it may be in an area devoid of major tributaries to the inferior vena cava. Thrombosis may then occur in the resulting stagnant cul de sac just cephalad to the umbrella. Although this procedure entails leaving a permanent foreign body in the vein, it has the advantage of avoiding surgery and anesthesia. The results so far have been excellent despite occasional reports of migration of the umbrella into a renal vein or pulmonary artery and embolism from the superior surface of the umbrella.[10] The procedure is especially well suited for older patients in whom the risk of surgery is considerable. It is advisable to continue anticoagulation, if it is not contraindicated, for at least a few months after umbrella insertion in order to diminish the chances of embolism from the superior surface.

SUPERFICIAL THROMBOPHLEBITIS

Thrombophlebitis of a superficial vein is easily diagnosed by inspection and palpation and is much more of an inflammatory lesion than deep vein thrombosis. One palpates a subcutaneous cord and finds surrounding tenderness, warmth and erythema. There may be localized swelling, but generalized edema of the leg never occurs with superficial phlebitis alone. A permanent fibrotic or calcified cord may result from this process, but the vein often recanalizes.

Superficial phlebitis tends to be self-limited, and treatment consists of warm soaks, rest and an anti-inflammatory agent such as aspirin or indomethacin. Although strict bedrest has been advocated in the past, this seems unwise especially in elderly people because it might lead to the development of deep vein thrombosis. All the anti-inflammatory agents must be used with caution because of their potential for causing upper gastrointestinal bleeding. We tend to avoid phenylbutazone except in very severe cases because of its occasional association with bone marrow depression. If phlebitis involves the greater saphenous vein with proximal extension to the mid-thigh, more rigorous therapy becomes necessary to prevent the thrombus from reaching the femoral vein, from which embolism can occur. The choice is between anticoagulation with heparin and ligation of the proximal saphenous vein in the inguinal area under local anesthesia. Since the latter is definitive, entails virtually no risk, and avoids the dangers of anticoagulation, we prefer this alternative especially in elderly patients.

The most important consideration in dealing with superficial phlebitis is its etiology. In all but a few cases, the lesion develops in a varicose vein as a result of the pooling of blood. This pooling is particularly common in elderly people because they are more prone to varicose veins and because they are more sedentary. Elastic support and elevation of the legs when sitting are the best ways to prevent recurrence.

In a small minority of cases, phlebitis occurs in a previously normal superficial vein. This should always be considered a harbinger of systemic disease. The possibilities include dysproteinemias such as cryoglobulinemia; myeloproliferative diseases such as polycythemia vera and primary thrombocytosis; collagen diseases; and cancer. In elderly people, the etiology is most likely to be an occult neoplasm or a myeloproliferative disease, and complete evaluation of the patient is mandatory.

CHRONIC VENOUS INSUFFICIENCY

Chronic venous insufficiency is almost always the result of previous episodes of deep vein thrombosis, either manifest or occult. An arteriovenous fistula is only rarely the etiology but should be considered if there is a history of trauma and if the venous insufficiency is entirely unilateral. In this situation, a bruit is generally heard. Chronic venous problems increase in incidence and severity with age and represent a significant cause of chronic disability in the elderly.

The cardinal signs of deep vein insufficiency are edema, varicose veins, hyperpigmentation, stasis dermatitis, and ulceration of skin. All result from valvular incompetence of deep veins and consequent gravitational, retrograde venous flow when the legs are below heart level. The edema is usually pitting in mild to moderate venous insufficiency but in long-standing severe disease, there may be secondary non-pitting lymphedema. Chronic edema per se contributes to this by stimulating fibrosis so that an end-stage, severely involved leg may contain a great deal of subcutaneous induration. In some cases, there may be rather marked venous stasis without much edema.

Hyperpigmentation is almost always present, characteristically located just above the medial malleolus and occasionally extending proximally as high as the mid-calf. The pigment consists of hemosiderin derived from the hemoglobin of red blood cells deposited subcutaneously as a result of increased venous and capillary pressures. It should not be confused with pigmentation along the shin, which is usually the result of recurrent trauma and is more common in older people. The location of stasis pigmentation corresponds to the area of highest venous pressure.

Stasis dermatitis and ulceration often appear together. The skin around the medial malleolus may become dry, scaly, and intensely pruritic. Subsequent scratching or other forms of trauma may lead to ulceration. In other cases, ulceration occurs spontaneously because of gradual erosion of subcutaneous tissue. Venous ulcers are characteristically hyperemic in contradistinction to arterial ulcers and almost always located at the medial ankle or somewhat more proximally.

Treatment of chronic venous insufficiency should be begun in its early stages to prevent disability secondary to either irreversible, bulky edema or recurrent ulceration. Most important is the use of elastic support and frequent elevation of the legs. Walking should be encouraged, but not standing still. In severe cases, elastic stockings should be individually tailored to the contour of the leg. If the patient does not note a marked diminution in edema after a night's sleep, he should be encouraged to sleep with his legs elevated four to six inches above heart level. Diuretics are of little value in managing venous edema. When ulceration is present, local infection is treated with warm soaks and local antibiotics.

VARICOSE VEINS

A varicose vein is simply a superficial vein aneurysm caused by valvular insufficiency and retrograde flow. It is important to distinguish between primary and secondary varicosities. A secondary varicose vein results from chronic deep vein insufficiency as the increased venous pressure is transmitted through the communicating veins into the superficial veins, overwhelming their delicate valves. Primary varicose veins, on the other hand, have nothing to do with disease of the deep

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veins. They tend to be hereditary, increase with age and child-bearing and probably represent congenital weakness of the venous walls. They are clinically significant only as a source of superficial phlebitis and occasional hemorrhage.

If other signs of stasis are present, the varicosities are obviously secondary. In the absence of edema or hyperpigmentation, the distinction can be made with a tourniquet. When the deep veins are completely competent, a tourniquet applied firmly enough to compress the superficial but not the deep veins should prevent retrograde flow when the patient stands. The varicosities should fill slowly (in 45 to 60 seconds). If the deep and communicating veins are incompetent, a tourniquet will not prevent rapid, retrograde filling because blood will flow, distal to the tourniquet, through communicating veins into the varicosities. The time required for venous filling with the tourniquet applied in several areas (mid-thigh, above knee, and below knee) is proportional to the degree of competence of the deep venous system.

The treatment of varicose veins is elastic support. Since edema, stasis and ulceration are the results of deep vein insufficiency, they are not likely to be benefitted by surgical removal of superficial veins. Furthermore, the cause of the varicosities (deep vein incompetence) remains, and they are likely to recur. Primary varicose veins can often be removed without recurrence, but this is rarely necessary. It follows then that venous stripping is essentially a cosmetic procedure that should never be contemplated unless a tourniquet test demonstrates at least partial competence of the deep veins. Venous stripping has virtually no role in the treatment of the elderly.

In summary, early recognition and appropriate treatment of venous disorders represent important challenges to the clinician. Appropriate medical intervention in the insidious processes of venous thrombosis and chronic venous insufficiency can save lives and prevent chronic disability.

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Coney Island Hospital
2601 Ocean Parkway
Brooklyn, New York 11235

Renal Disease in the Elderly

*Herman Rosen, M.D., F.A.C.P.**

Several studies have shown that renal function declines with advancing age. The clinician treating elderly patients with significant kidney disease must therefore be aware of this underlying alteration of renal function. Because the kidney has considerable functional reserve, the senescent kidney per se is not generally the cause of clinically significant symptomatology. However, under conditions of concomitant illness or other stress, the increased demands upon the kidney may be such that the kidney cannot adequately or promptly respond. Thus alteration in fluid and electrolyte balance or other manifestations of kidney insufficiency may be more readily observed in the older than in the younger individual.

HISTOLOGICAL AND FUNCTIONAL CHANGES

In the elderly the kidneys show degenerative changes in the tubules especially in the proximal convoluted tubule, with cloudy swelling, atrophy of tubular walls, and tubular collapse. Other tubules are dilated. Fibrotic changes are seen in the glomeruli with hyalinization in some. These changes are presumably due to structural changes in the renal vasculature. Arteriolar hyalinization and intimal thickening in the small arteries as a result of proliferation of elastic tissue have been observed in kidneys from elderly individuals. These vascular alterations are also noticed in hypertension, but they are seen in the kidneys of the elderly even in the absence of hypertension. Intimal hyperplasia develops in the larger arteries of the kidneys, but this process is often complicated by atherosclerosis.

Along with the anatomic and biochemical changes in the aging kidney, certain changes in renal function occur. Glomerular filtration rate declines after the age of 40 at approximately 1 per cent per year. Renal plasma flow similarly declines with advancing age. Tubular function appears to decline at a rate comparable to glomerular filtration rate, so that glomerulotubular balance is not significantly altered. The uniform

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Chief, Nephrology Division, Coney Island Hospital; Associate Professor of Clinical Medicine, State University of New York, Downstate Medical Center, Brooklyn, New York

loss of glomerular and tubular function has been interpreted as a loss of nephrons with age.

Studies of the renal handling of water in the elderly indicate an impairment in urinary concentrating and diluting ability. Maximum urinary concentration after dehydration or administration of a test dose of vasopressin may be significantly altered in the elderly. The maximum rate of urine flow may be reduced. The minimum dilution of urine may also be impaired.

Acid-base measurements in the elderly show normal blood pH and bicarbonate values under resting conditions. However, under an acid-loading challenge, the response of the kidney among elderly patients is considerably slower than among younger individuals. A similarly reduced rate of response is observable with alkali loads. Plasma electrolyte composition is normal under basal conditions in the elderly, but under stress, these individuals may readily develop electrolyte abnormalities. The detailed renal handling of calcium, magnesium, and potassium in the elderly has not been studied in depth.

EVALUATION OF THE PATIENT WITH RENAL DISEASE

Signs and Symptoms

The elderly patient is likely to have illnesses that adversely affect kidney functions. The primary disorder may not be a renal disease but rather one of another organ, such as myocardial infarction or gastrointestinal bleeding. Presenting symptoms may be that of the underlying disorder or manifestations of diseases of the urinary tract. Certain symptoms such as dysuria, polyuria, or gross hematuria obviously indicate urinary tract problems. Other signs and symptoms such as nausea, anorexia, weakness, anemia or unexplained fever, though not directly involving the urinary tract, may nonetheless be related to underlying renal disorders. Patients with unexplained edema or hypertension must be screened for renal disease. The patient with severe renal disease may present with neurologic manifestations such as convulsion, coma, asterixis, tremor, or headache. Bleeding because of a qualitative platelet defect may be an initial sign of uremia.

Laboratory Data

An important indication of renal disease is the presence of proteinuria. Protein excretion in the urine of more than 150 mg per day is abnormal and should not be dismissed as a benign manifestation of the senile kidney. The mean blood urea nitrogen concentration in a group of normal individuals whose average age was 75 years was 22.5 mg per 100 ml and ranged from 9 to 43. The known effect of increased dietary protein or heightened catabolism on elevating blood urea nitrogen is somewhat exaggerated in the elderly. Serum creatinine concentration itself, however, is not much elevated. In this same group of 35 normals, serum creatinine averaged 0.9 mg per 100 ml and ranged from 0.5 to 1.4. Creatinine clearance, an estimate of glomerular filtration rate, is uniformly reduced. In a group of 21 elderly individuals without renal disease or hypertension, the mean creatinine clearance was 53 ml per minute. It is noteworthy that even though glomerular filtration rate is diminished, serum creatinine was below 1.5 mg per 100 ml in all subjects and below 1.0 mg per 100 ml in 70 per cent. A normal serum creatinine level with diminished renal function indicates reduced production of creatinine compared with younger subjects. Creatinine is produced in proportion to muscle mass; the lower production probably reflects muscle atrophy attributable to the sedentary existence of the group studied. In the face of reduced creatinine production in the elderly patient, the serum creatinine level in uremia may not reflect the severity of renal functional impairment. Moreover the ratio of blood urea nitrogen to creatinine may be higher than in a younger individual on a normal diet.

Radiography of the Kidneys

In the evaluation of the patient with renal disease, an intravenous pyelogram can provide information on the size and contour of the kidneys as well as the structure of the calyceal system. The caliber and course of the ureters can be visualized. In patients with moderate reductions in glomerular filtration rate, high-dose infusion pyelography may permit visualization of the urinary tract. The usefulness of this procedure can be enhanced by laminography. When glomerular filtration rate is less than 10 ml per minute, the likelihood of pyelographic visualization of the kidneys is greatly reduced, but laminography alone may reveal kidney size and contour. It is important not to dehydrate the patient in preparation for pyelography. The defect in concentrating ability of the elderly kidney exaggerated by a reduction in glomerular filtration rate can lead to a failure to conserve water. There may then be excessive fluid loss, consequent dehydration, and further embarrassment of renal function.

The length of the renal shadows in the elderly seen on x-ray examination appears normal and equal bilaterally—at least three times as long as the second lumbar vertebra and its disc. However, a longitudinal study to see if kidney length diminishes with age has not been done. In contrast to urography, renal scan using chlormerodrin labelled with isotopic mercury showed significant abnormality in 70 per cent of elderly patients studied. Abnormalities included asymmetric areas of decreased uptake and planimetric examination of the scans showed frequent inequality of the two kidneys and considerable reduction of active kidney area. These scan defects may represent ischemic areas of the kidney where tubular function is sharply reduced. Whatever the cause, kidney scan abnormalities are to be expected in the elderly and as isolated findings in an asymptomatic patient should not be a cause for alarm.

Urinalysis

In the evaluation of the patient with suspected renal disease, the examination of a fresh clean voided sample of urine can be of considerable value. This should be done by the physician because he is best able to correlate urinary findings with the clinical picture. In the examination of the urinary sediment, a comment about technique is in order. A 15 ml sample of urine, preferably a concentrated specimen, is centrifuged for 5 minutes at 3000 rpm. The sediment is transferred via a Pasteur pipet to a microscope slide and a cover slip is applied. For routine purposes, examination of the unstained sediment suffices, but staining with dye such as that described by Sternheimer and Malbin can be done to clarify the identity of formed elements.

Gram stain and culture of the urine should be done if urinary infection is suspected. In a survey of 35 aged patients, approximately one third had pyuria (more than 5 white blood cells per average high-power field). Half the patients with pyuria had bacteriuria. The presence of more than 2 red blood cells per high-power field is abnormal and bears further investigation. Certain formed elements in the urine have refractive indices close to urine itself and may not be seen against the background unless the level of light in the microscopic field is reduced. These include hyaline casts and vaginal cells. The presence of vaginal cells (Fig. 1) can be of importance in alerting the physician that any culture of that urine specimen will be contaminated by vaginal flora. The presence of large numbers of bladder epithelial cells is suggestive of cystitis. These transitional cells contain small nuclei and fairly clear cytoplasm. They can be readily recognized by their ovoid shape, often interdigitating with each other (Fig. 2). Renal tubular epithelial cells are smaller, with larger, round eccentric nuclei and with numerous cytoplasmic inclusions (Fig. 3). These cells are seen in great number in acute tubular necrosis, glomerulonephritis, and other renal diseases. When cells such

Figure 1. Vaginal cells (500×).

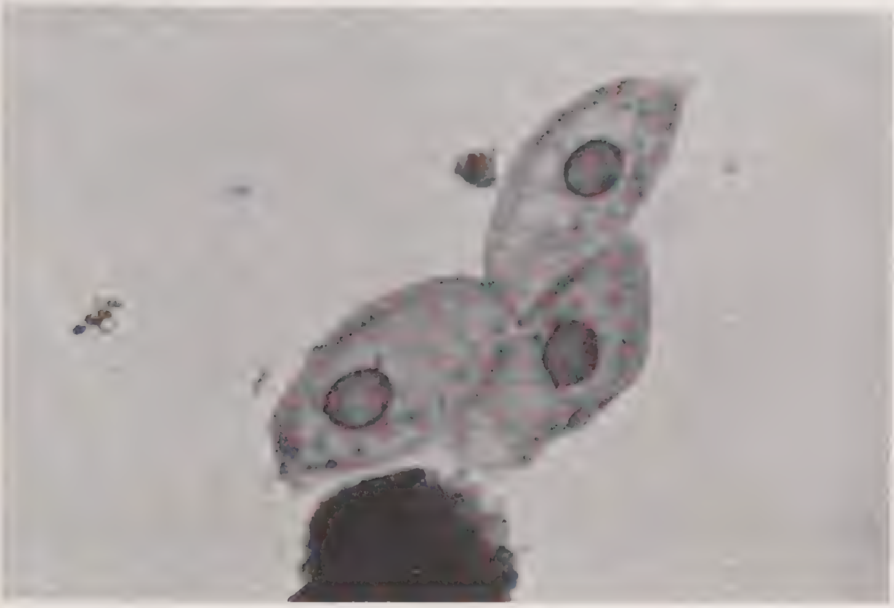

Figure 2. Bladder cells (500×).

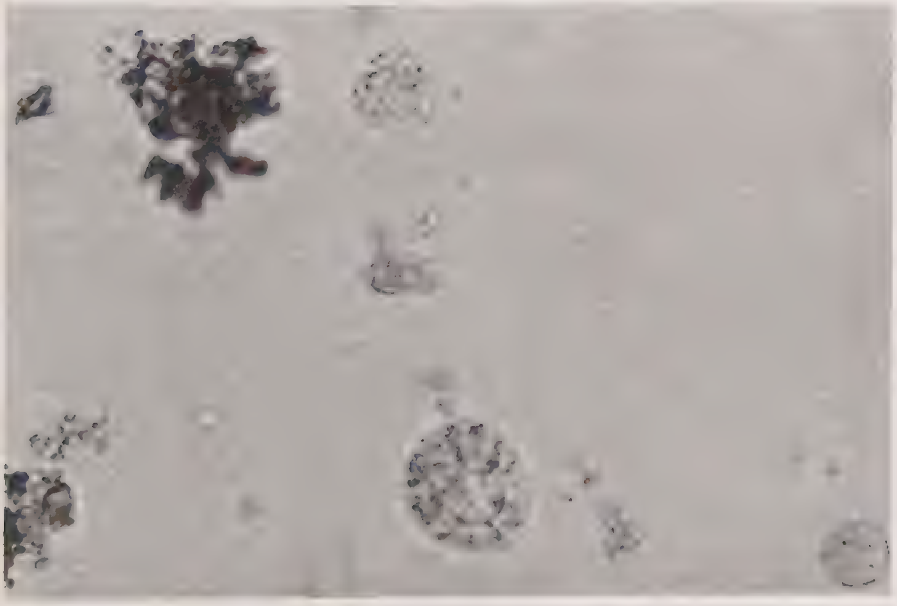

Figure 3. Renal tubular epithelial cells (500×).

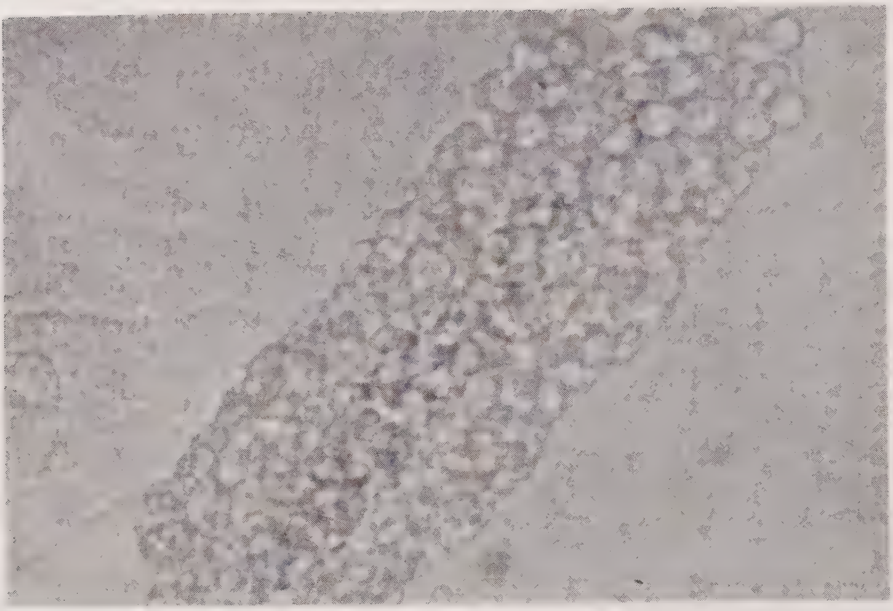

Figure 4. Red blood cell cast (500×).

as red cells are incorporated within the substance of a cast, it is indicative that the cells became embedded in the lumen of the renal tubule distal to the loop of Henle. Red blood cell casts (Fig. 4) signify bleeding from the kidney such as in acute glomerulonephritis, lupus nephritis, or malignant hypertension.

URINARY TRACT INFECTION AND OBSTRUCTION

Urinary tract infection in its various forms is the most common type of renal disease. This is particularly so in old age; the incidence of pyelonephritis appears to increase with advancing age. In the elderly, pyelonephritis appears to be somewhat more frequent in men. In the younger groups women are predominantly affected. Possible reasons for this increasing incidence of infection in the elderly are several. Vascular insufficiency may predispose to infection of the kidney. Urinary stasis and obstruction are known to favor persistence of bacteria in the kidney following bacteremia. In addition to the hematogenous route of infection, ascending infection, especially in the presence of urinary stasis, is a prominent mode of infection. Even in the absence of obstruction, vesicoureteral reflux has been implicated in pyelonephritis.

Prostatic Obstruction

An important cause of obstructive uropathy in elderly men is prostatic disease, both benign hypertrophy and carcinoma. Unless contraindicated, rectal examination of the prostate should be performed in all men. One should remember that this examination may not detect enlargement of the median lobe of the prostate. A relatively benign, noninvasive method of detecting prostatic enlargement and its obstructive effects is to take a post-voiding film at the termination of intravenous pyelography and to observe the prostate and estimate the amount of residual urine. If the prostatic enlargement is causing obstructive damage to the urinary tract (worsening hydronephrosis or declining renal function) or symptoms attributable to reduced bladder capacity, then surgical intervention is indicated. A large prostate as an incidental finding is not in itself an indication for prostatectomy. Similarly the presence of a residual volume of urine in the bladder may not need to be treated by indwelling catheterization. If the urine is sterile, invasive procedures may induce bacteriuria and worsen the situation. Instead a program of frequent voiding or double voiding may reduce moderate degrees of bladder distention.

Indicators of Urinary Obstruction

In the evaluation of a patient with unexplained renal impairment, obstructive uropathy should be considered since this disorder may be reversible. It is not generally appreciated that urine volume may be greater than normal in partial obstruction of the urinary tract possibly because of impaired concentrating ability. Patients with polyuria caused by incomplete obstruction may also have polydipsia, thus mimicking symptoms of diabetes mellitus. Dribbling incontinence may be due to chronic urinary retention, bladder enlargement, and overflow. With less severe bladder distention, the presenting symptoms may be frequent voiding of small amounts of urine. Urinary infection frequently accompanies obstruction. Infection under these circumstances may be refractory to antibiotic therapy. Therefore obstructive lesions should be considered in patients with repeated or persistent urinary tract infections.

There are those who say that the increased incidence of pyelonephritis in elderly men is seen only after genitourinary instrumentation. It is well known that following bladder catheterization, there is approximately a 5 per cent incidence of infection. With indwelling catheters the incidence rises to over 90 per cent. Therefore catheterization of elderly patients should not be routinely performed. It is not wise to place a catheter in a patient's bladder just because the patient is confined to bed. On the other hand, when indwelling catheterization is indicated, such as in severe urethral obstruction, this procedure should not be withheld. If a retention catheter is inserted, aseptic technique must be adhered to. The catheter should then be connected to a closed sterile drainage set. If catheterization will be required for more than a day or two, a continuous antibacterial rinse using dilute neomycin-polymyxin B or other suitable irrigant should be used.

When urinary tract infection is acute and causing severe discomfort and systemic symptoms, its major importance in the clinical setting is obvious. However it is easy to overlook the presence of a smoldering infection such as cystitis. With cystitis there may be no constitutional symptoms, just frequency and dysuria. There may be hematuria and pyuria and the urine may be foul-smelling. Treatment should be appropriately instituted. The importance of detecting and treating cystitis is related not so much to its potential for serious consequences. Rather, its importance lies in the relief of the discomfort or urgency, nocturia, or dysuria which interfere with the sleep, rest, or morale of the elderly patient.

OLIGURIA IN THE HOSPITALIZED PATIENT

When urine flow is less than 400 ml per 24 hours, signs of impaired renal function rapidly ensue. A search for reversible causes of the oliguria must be undertaken.

Oliguria from Obstructive Uropathy

Obstruction of the urinary tract must be considered in all cases of anuria or oliguria. Urethral obstruction can be checked for by examining the patient and ascertaining if the bladder is distended. On occasion, hospitalized patients can suffer urinary retention merely because of confinement to bed. Elderly men with marginal prostatic enlargement may need the additional support provided by gravity with micturition in the upright posture. When a patient is put to bed, his bladder may not have sufficient muscular force for him to void in the reclining position. This effect may be exaggerated in the elderly patient who is sedated and may not be aware of his distended bladder. With overdistention of the urinary bladder, decompensation of the urinating mechanism can occur and the patient is then unable to void. Antihistamines may alter the muscular activity of the bladder and lead to urinary retention in susceptible individuals. If the clinician can diagnose obstruction of the urethra as the cause of oliguria, then the obstruction must be relieved promptly by urethral catheterization or suprapubic cystostomy until specific definitive therapy is available. Care must be taken to drain the overdistended bladder slowly. In cases of rapid decompression, hemorrhage from the bladder or syncope has been seen.

Obstruction of the ureters, such as by calculi or neoplasm, should be looked for. If one is not sure that there is end-stage renal disease, indicated by small contracted kidneys on abdominal films, contrast visualization of the kidneys and ureters should be attempted. When excretory pyelography is not possible, it may be necessary to perform cystoscopy and retrograde pyelography of one kidney to ascertain the patency of the urinary tract.

Oliguria from Prerenal Causes

When the oliguria is not due to obstruction, one should next consider prerenal causes. If there is circulatory insufficiency because of cardiogenic shock or hemorrhage, measures should promptly be undertaken to correct these conditions. It is possible, especially in the elderly patient, to miss evidence of hypovolemia. Clues to the possible presence of hypovolemia can be found in a reduction in blood pressure and tachycardia especially when the patient assumes the upright posture. Dehydration in the elderly may not be readily apparent because the usual signs are not always reliable. Skin turgor may be poor without dehydration and a dry tongue may represent mouth breathing. Nevertheless dehydration should be thought of as a cause for oliguria.

In the differential diagnosis of oliguria, the laboratory examination of the urine can provide significant diagnostic help. In oliguria due to prerenal causes, one should expect urinary osmolality to be elevated above values of 800 mOsm per kg. However, if the kidney has had an age-related reduction in urine concentrating ability, then urinary osmolality may not be elevated above 500 mOsm per kg. In this instance a reduction in urine sodium concentration below 30 mEq per liter speaks for prerenal azotemia.

When oliguria is caused by decreased circulatory volume, and there is no danger of congestive heart failure, volume should be restored with parenteral fluid containing sodium (physiological saline or fractional saline solutions). To test this diagnosis further, 12.5 or 25 gm of mannitol can be given intravenously in 5 to 10 minutes, and urine volume monitored to see if output increases.

If, however, the venous pressure appears clinically to be elevated or if congestive heart failure is imminent, then mannitol should not be given but alternatively a test dose of furosemide (40 mg) can be tried. A prompt diuretic response to this drug suggests prerenal azotemia, but in rare instances, patients with acute renal failure may also have increased urine output. It should be noted that a urine sample should be obtained before these therapeutic trials are instituted. The diuretic can alter urine concentration and sodium content making the interpretation of these findings impossible.

Oliguria Caused by Intrinsic Renal Disease

If prerenal causes for oliguria have been ruled out, one must then consider acute renal failure. This diagnosis will be supported by the finding on urinalysis of proteinuria and sediment containing red cells, renal tubular cells, white cells, casts of these cells, and granular casts. The urine will be isosthenuric and contain sodium at a concentration greater than 40 mEq per liter. In a hospitalized setting, one must consider nephrotoxic drugs such as the aminoglycoside antibiotics as possible causes of acute renal failure. Potentially nephrotoxic drugs must be discontinued or reduced in dosage. In cases with unexplained renal failure, it is wise to check the serum calcium level. Hypercalcemia by itself can damage the kidneys. Serum calcium elevation may occur in an elderly patient who is confined to bed. The effect of weight bearing on bone stimulates bone formation. In an instance where a patient is hospitalized and confined to bed, normal bone resorption continues but bone formation diminishes. This imbalance can lead to hypercalcemia. The patient with Paget's disease of bone is particularly susceptible to hypercalcemia. When hypercalcemia is present, prompt lowering of the serum calcium should be undertaken by administering saline solutions, phosphate therapy, calcitonin, or possibly dialysis with low calcium solutions.

Acute Renal Failure

In time, acute renal failure due to intrinsic disease such as tubular necrosis is likely to be reversible. Therefore it is of utmost importance that the patient receive proper supportive therapy in this illness. The oliguria is generally profound early in the course of acute renal failure. The physician should therefore not try to force a diuresis. If unrestricted fluid is permitted, edema and hyponatremia can ensue. The elderly patient may be particularly prone to cardiovascular problems such as pulmonary edema or severe hypertension during the oliguric phase. Hyperkalemia may occur especially if there is increased catabolism or considerable tissue damage because of anoxia or dehydration.

The oliguric phase passes into the diuretic phase of acute renal failure. In this situation, proper fluid replacement is essential to maintain homeostasis. It should be noted that although this disease can be reversible, it still carries a high mortality rate and a high incidence of persistent renal abnormalities, especially in the elderly patient with underlying disease.

RENAL CALCULI

Kidney stones are a frequent cause of morbidity in the elderly. When the presenting complaint is renal colic, the diagnosis is readily apparent. The presenting symptoms may be those of infection, obstruction, or hematuria. In some instances the initial presentation is one of renal insufficiency without pain. An x-ray film of the abdomen or intravenous pyelogram will be diagnostic.

When the diagnosis is evident, initial management may be medical or surgical. In any case, it is important for the physician to try to determine the composition of the stone so that he can take appropriate measures to prevent recurrence. If possible the stone should be obtained for analysis. If the stone is not available, then a clue to its composition may be obtained from the observation of crystal forms in the urinary sediment. For example, uric acid crystals in the sediment (Fig. 5) suggest that the stone is made of uric acid. In the elderly, over 90 per cent of renal calculi contain calcium, generally as the oxalate. Fewer than 10 per cent will be uric acid stones. A small percentage will be cystine stones (Fig. 6), their incidence being higher in the younger age group.

Kidney stones are formed in two main clinical settings. First, the urinary composition of certain stone-forming crystalloids may be increased in concentration or amount, such as in hypercalciuria, arising from various causes. Second, at normal crystalloid concentration, anatomical or chemical changes conducive to stone formation may be present. Persistent aciduria leading to uric acid stones falls into this category.

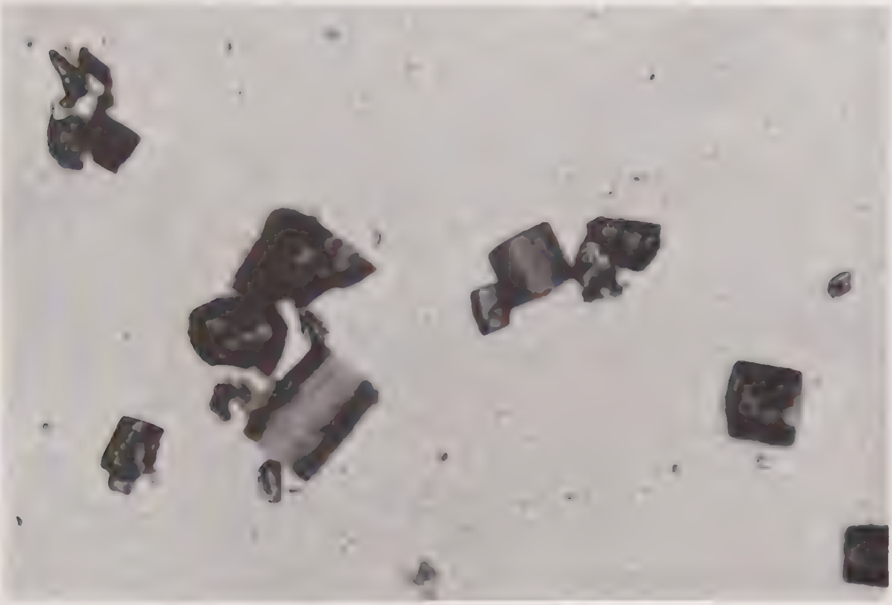

Figure 5. Uric acid crystals (500×)

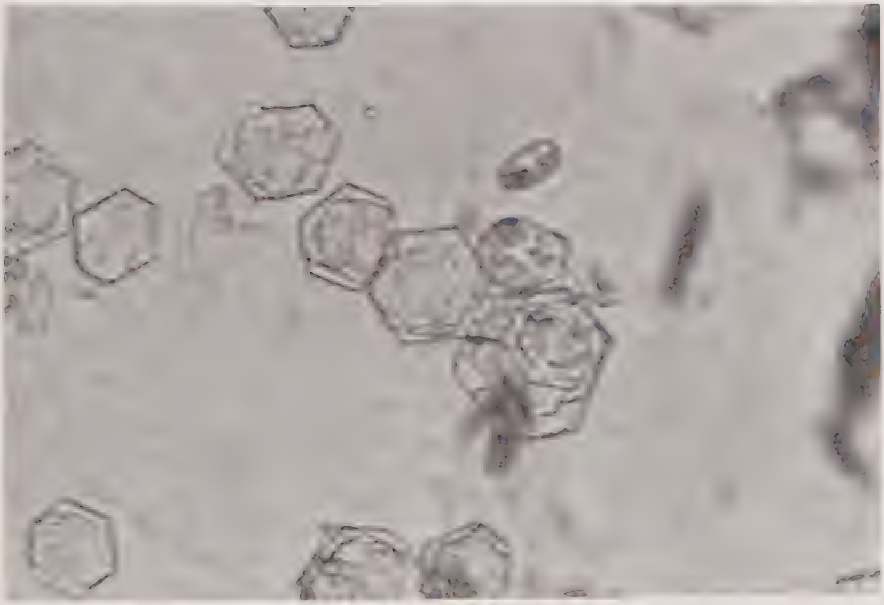

Figure 6. Cystine crystals (500×).

Calcium Stones

If a calcium stone is found, a 24 hour collection of urine should be analyzed for hypercalciuria. In general, hypercalciuria can be defined as the excretion of more than 250 mg of calcium per day on a diet without milk or dairy products. Most patients with calcium stones excrete normal amounts of calcium. However, when hypercalciuria occurs, one should consider conditions which cause dissolution of bone such as hyperparathyroidism, multiple myeloma, metastatic cancer, senile osteoporosis, immobilization, Paget's disease, renal tubular acidosis, and corticosteroids. Hypercalciuria may also be related to increased calcium absorption such as in vitamin D intoxication. Measures to prevent stone recurrence will depend on the etiology. In all cases, however, even where the etiology is not clear, increased water intake may be beneficial.

Uric Acid Stones

Uric acid nephrolithiasis occurs in gout and in hyperuricemic states such as polycythemia vera and myeloproliferative disorders. These patients have hyperuricosuria. Other patients with uric acid stones do not have increased excretion of urate but rather have increased urine acidity. This persistent aciduria may be noted in chronic diarrheal states or may represent a renal tubular defect in which ammonia production is sharply reduced. Patients with hyperuricemic conditions often stop forming stones after taking allopurinol, which inhibits uric acid synthesis. Persistent aciduria may respond to appropriate provision of alkali to raise urinary pH. Again, increased water intake may help to reduce stone formation.

HYPONATREMIA

In a medical service of a hospital with a predominantly elderly population, we have been impressed by the relatively large number of patients we have seen with hyponatremia—reduction of serum sodium concentration below 133 mEq per liter. Many of these patients are not symptomatic from this hyponatremia, but it is possible that the hyponatremia may amplify symptoms from the patient's underlying disorder. Symptoms, when they occur, are not specific and include lethargy, mental sluggishness, anorexia, headache, and nausea. Convulsions and coma may ensue when hyponatremia is severe.

Proper therapy for this disorder requires an adequate diagnostic approach. When the hyponatremia appears to be associated with an excess of body fluid, one should think of congestive heart failure or cirrhosis. Here salt retention is primary and water retention follows. In these edematous states, total body water is increased but the effective arterial blood volume may actually be reduced.

Conversely, when hyponatremia is associated with a reduction in body fluids and salt content, one should consider losses of fluid and electrolyte. Losses can be renal or extrarenal. Extrarenal depletion of salt occurs with diarrhea or vomiting. Renal salt wastage can occur in a variety of chronic renal diseases, adrenal insufficiency, or with administration of diuretics. Urine sodium concentrations indicate the extent of renal losses and are usually greater than 20 mEq per liter. It is important to remember that patients with renal failure generally cannot conserve sodium unless they are oliguric, and they may become depleted on a low-salt diet.

A diagnosis of inappropriate secretion of antidiuretic hormone can be made when the hyponatremia is accompanied by inappropriately elevated urine osmolality, generally greater than 100 mOsm per kg, along with urine sodium concentration greater than 30 mEq per liter. The patient should have normal hydration with no more than a trace of edema, and normal renal and adrenal function to make the diagnosis on simple clinical criteria.

Certain drugs can cause hyponatremia. Chlorpropamide may potentiate vasopressin. Diuretic agents can induce hyponatremia both by impairing renal diluting ability and by depleting salt and water. On occasion, water retention may mask signs of volume depletion caused by diuretics.

In some instances hyponatremia may be spurious. With hyperglycemia, the glucose-related hyperosmolality of the extracellular fluid is associated with shifts of water from cells to extracellular fluid, thereby diluting the extracellular fluid sodium concentration. In marked hyperlipidemia, the hyponatremia is related to the volume in the plasma occupied by the circulating lipid. The concentration of sodium in plasma water is normal.

The treatment of hyponatremia will depend on its etiology. Obviously, salt should not be given to the edematous patient with cardiac failure or hepatic insufficiency. Rather the patient should be treated by restriction of fluids below the level of insensible losses and urine output. Similarly in the syndrome of inappropriate secretion of antidiuretic hormone, water restriction is the treatment of choice. In depletional hyponatremia, isotonic saline infusion is indicated. No treatment is necessary for the pseudohyponatremia caused by hyperlipidemia. When hyperglycemia causes hyponatremia, control of blood glucose will restore sodium concentrations.

If hyponatremia from any cause is associated with serious symptoms of water intoxication such as coma, convulsions, or progressive stupor, then hypertonic saline infusions can be given. The salt solutions should be cautiously given to elderly patients in quantities calculated to raise sodium concentrations to approximately 120 to 125 mEq per liter. At this level of sodium concentration serious symptoms are not likely. The clinician can then treat with appropriately conservative therapy.

Hyponatremia in the elderly can thus be divided into three categories—depletional, dilutional, and pseudohyponatremia. Only in the depletional category is salt administered. Dilutional states can be treated with fluid restriction. Pseudohyponatremia requires no treatment directed at the sodium level.

CHRONIC RENAL INSUFFICIENCY

When renal insufficiency is present, the physician must seek and properly treat reversible causes. However, if no reversible factors are present, then the patient must be treated for end-stage renal disease. We have been gratified by the satisfactory response seen with the use of conservative and dialysis techniques in older patients. In the elderly uremic patient with moderate but not severe renal failure, symptoms such as nausea and lethargy may be controlled by reduction of protein intake to 30 or 40 gm daily. Sufficient calories must be supplied as carbohydrate and fat. Further symptomatic improvement may be obtained if the protein in the diet is of high biologic value (eggs) and unessential amino acids are eliminated. Proper amounts of salt and fluid must be provided in the diet to restore normal values and to replace losses in the individual patient.

When these conservative measures, properly applied, are not sufficient to control symptoms of uremia, intermittent dialysis must be considered. When chronic hemodialysis therapy was first introduced, its availability was limited by a paucity of facilities. Many patients with end-stage renal failure were treated with occasional peritoneal dialysis as an adjunct to conservative therapy. This combined treatment regimen often palliated our elderly patients sufficiently to permit them to lead a pleasant albeit sedentary existence. Peritoneal dialyses could be performed every 7 to 10 days and the patient returned to his home setting in the interval.

As the number of hemodialysis beds has increased, we have been placing more elderly patients with end-stage kidney disease on such therapy. By and large these patients have responded well to hemodialysis. However, it has been noted that the incidence of cardiovascular morbidity in all patients on hemodialysis is enormous and is often a determining factor in survival. This increased mortality is especially high in elderly patients with overt or latent heart disease. Reasons have been advanced for this acceleration of degenerative cardiovascular disease in uremia. It is clear that uremia is often associated with several risk factors for atherosclerosis: hypertension, glucose intolerance, and hyperlipidemia, especially hypertriglyceridemia. In addition a patient can have coincidental "azotemic arteriopathy"—widespread arterial calcification probably related to elevated serum phosphate levels and secondary hyperparathyroidism. Diligent effort by the physician is required to identify and treat these risk factors. Hypertension is almost universally found in elderly uremic patients and can usually be managed with standard antihypertensive agents and prudent dialysis. Hyperlipidemia should be treated with diet manipulation and lipid-lowering drugs. Hyperphosphatemia can be treated by low-phosporus diets and oral administration of phosphorus binding gels such as aluminum hydroxide.

The physician must be on the alert for other complications that elderly dialysis patients are prone to. Problems of vascular access because of sclerotic blood vessels are to be anticipated. Congestive heart failure may occur in patients with large fistulas that have been surgically created to obtain vascular access for dialysis. The dosage of heparin used in dialysis must be carefully regulated since bleeding in the elderly patient may have catastrophic consequences. All in all, satisfactory results may be happily obtained in the treatment of the elderly patient when the physician and his patient are properly motivated.

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Nephrology Division
Coney Island Hospital
2601 Ocean Parkway
Brooklyn, New York 11235

Aging and the Respiratory System

Santi Dhar, M.D., Subramaniam R. Shastri, M.D.,** and Robolge A. K. Lenora, M.D.****

Because of the availability of sophisticated, non-invasive tests of pulmonary physiology, a great deal is known about changes in lung function with age. It is difficult, however, to separate changes strictly due to the ravages of time from the effects of environmental factors. The longer one lives, the longer one's lungs are exposed to such slowly acting toxins as tobacco and pollution, which lead gradually to respiratory deterioration. A heavy cigarette smoker would be subject to this risk even if his lungs remained young, but functional changes related to aging make matters worse.

Several studies have shown age-related morphologic changes in the respiratory system. A triad of findings accounts for most of the changes in pulmonary function: (1) loss of elastic tissue surrounding alveoli and alveolar ducts, (2) increased anteroposterior diameter of the chest owing to rib and vertebral decalcification, and (3) weakening of respiratory muscles.

As a result of these changes, forced vital capacity (FVC) and one-second forced expiratory volume (FEV_1) diminish progressively with age. FEV_1 peaks at about age 25 and then declines progressively at a mean rate of 32 ml per year for men and 25 ml per year for women.[14] The FEV_1/FVC ratio also decreases, reaching a mean of 77 per cent for individuals 45 to 49 years old and 71 per cent at age 64.[20] The rapidity of change in vital capacity is apparently a reflection of general health because the Framingham study showed an inverse relationship between vital capacity and probability of death within 10 years (Fig. 1).[3] A more recent study demonstrated a direct relationship between diminished vital capacity and likelihood of suffering a myocardial infarction. This finding was independent of other risk factors such as smoking.[11] Maximum breathing capacity (MBC), which reflects the bellows action of the chest, decreases even more, falling to 50 percent by age 60.[12] This is primarily the result of weakened respiratory muscles. That changes in FEV_1 and MBC are not secondary to bronchial obstruction is indicated by

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*Chief, Pulmonary Disease Division, Coney Island Hospital, Brooklyn, New York
**Fellow, Pulmonary Disease Division, Coney Island Hospital, Brooklyn, New York
***Fellow, Pulmonary Disease Division, Coney Island Hospital, Brooklyn, New York

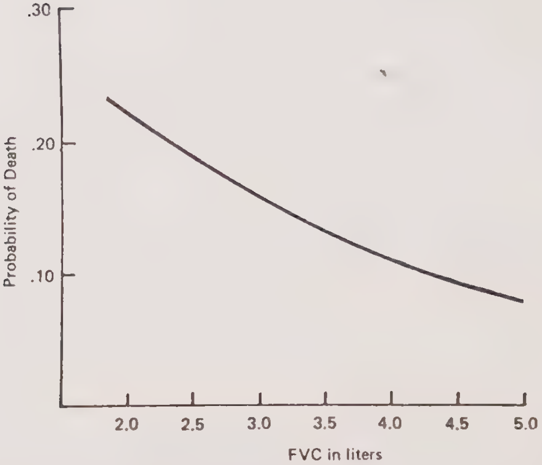

Figure 1. Smoothed probability of death in 10 years by forced vital capacity in men ages 50–59. Framingham Heart Study. (*From* Ashley, F., Kannel, W., et al.: Ann. Intern. Med., 82:739-745, 1975. Reprinted with permission.)

relatively normal values for airway resistance in normal elderly subjects.

Loss of elastic recoil is responsible for three other changes in pulmonary function tests: increases in residual volume, compliance, and "closing volume." Compliance, defined as change in lung volume per unit change in intrapulmonary pressure, tends to become frequency-dependent in the elderly; i.e., it decreases with increasing respiratory rate. These changes lead to uneven ventilation.

"Closing volume," the lung volume at which small airways start to close, increases linearly with age.[2] When "closing volume" approaches functional residual capacity, intrapleural pressure becomes positive in the lower lung zones, exceeds airway pressure, and forces small airways at the lung bases to close earlier. Since the intrapleural pressure at the apex is always 7.5 cm H_2O lower than at the base in the upright position, the upper zones still have negative intrapleural pressure, and their airways remain open. Consequently, with normal tidal volume breathing, most ventilation takes place in the upper zones. Since pulmonary blood flow continues to favor the capillaries of the lower zones, the elderly have a significant disproportion between ventilation and perfusion, which results in an increased alveolar-arterial oxygen gradient and a decrease in arterial oxygen tension. Arterial oxygen tension (Po_2) declines linearly with age, reaching a mean of 75 mm Hg in the seventh decade (Fig. 2).[16] Most elderly people can raise their Po_2 by breathing deeply to minimize early airway closure.

Changes within the pulmonary circulation—loss of capillaries, intimal fibrosis, and decreased pulmonary artery distensibility—probably have no significant effect on oxygenation. Pulmonary artery pressure, although normal at rest, rises abnormally with exercise in the elderly.[10]

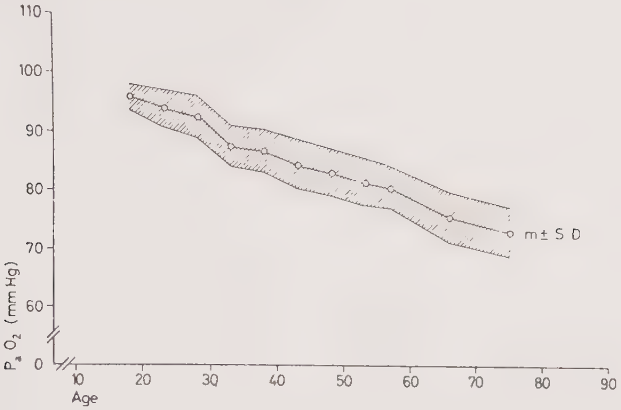

Figure 2. PaO_2 mean values and standard deviations in relation to age in 11 progressive age groups. (*From* Sorbini, C. A., Grassi, V., Solinas, E., et al.: Respiration, 25:3-13, 1968. Reprinted with permission.)

Because of a diminished number of capillaries, diffusing capacity decreases, falling as much as 60 per cent by age 70. The decline occurs faster in men than in women and is greater in the supine than in the seated position.[17]

This physiologic background is useful in understanding the impact of chronic respiratory disease on the elderly.

CHRONIC OBSTRUCTIVE LUNG DISEASE

With increasing cigarette smoking and air pollution, the incidence of chronic obstructive lung disease (COLD) is increasing all over the world. It is conservatively estimated that 30,000 deaths a year result from COLD in the United States alone, and there is untold suffering among the survivors. Even though this disease probably starts at an early age, the patients rarely present themselves before they are in their 40's. COLD can be divided pathophysiologically into two main categories: chronic bronchitis and emphysema.

Chronic bronchitis, histologically, is characterized by mucus gland hyperplasia in the large airways, goblet cell hyperplasia, chronic inflammation, and mucus plugging in small airways. These changes lead to uneven ventilation of the alveoli and mismatching of ventilation and perfusion (V/Q). Physiologic consequences are alveolar hypoventilation leading to hypoxia and carbon dioxide retention.

Emphysema is defined as abnormal enlargement of the air spaces distal to the terminal bronchiole, accompanied by destructive changes of alveolar walls. Emphysema is of two varieties: (1) Centilobular emphysema shows primarily destruction and confluence occurring in the region of the respiratory bronchioles. It is commonly associated with cigarette smoking and chronic bronchitis. (2) Panlobular emphysema

Table 1. *Differential Diagnosis of Emphysema and Chronic Bronchitis*

	"PINK PUFFER" EMPHYSEMA TYPE A	"BLUE BLOATER" CHRONIC BRONCHITIS TYPE B
History	Smoking history. May have family history of lung disease, e.g., antitrypsin deficiency.	Smoking history. Frequent history of congestive heart failure.
Clinical	Thin body build. May have marked weight loss. Dyspnea but no cyanosis ("pink"). No history of congestive heart failure except terminally. No or scanty sputum production.	Chronic cough, sputum production, cyanosis, and evidence of right heart failure. Stout body build.
Radiology	Flattening of diaphragm and increase in retrosternal airspace (2.5 cm on lateral film). Long narrow heart and deficient pulmonary vascular markings on posteroanterior film.	Increased bronchovascular markings, so called "dirty lung." Evidence of right ventricular enlargement.
Laboratory Findings	No secondary polycythemia.	Secondary polycythemia.
Physiology	TLC* = increased.	Normal or increased.
	FEV_1* = decreased.	Decreased but may improve with bronchodilator.
	Diffusion – markedly decreased.	Normal or decreased.
	pH = normal.	Normal or acidic.
	Pco_2 = usually low or normal until terminal stage.	High.
	HCO_3 – normal.	High.
	Po_2 – $>$ 60 mm Hg but decreases on exercise.	$Po_2 < 60$ mm Hg but may improve with exercise.
Clinical Course	Gradual deterioration of symptoms.	Repeated chest infections and right heart failure.

*TLC – total lung capacity
*FEV_1 = forced expiratory volume in one second.

involves the whole acinus, i.e., the area from the respiratory bronchiole to the alveolar sac.

In emphysema, loss of elastic recoil due to alveolar destruction leads to increased airway resistance, particularly in small airways, even without any intrinsic obstructive lesion. The capillary network in emphysema is destroyed along with alveolar walls, so that ventilation/perfusion is better maintained than in chronic bronchitis. This may account for the normal arterial P_{CO_2} and only mild hypoxemia in emphysematous patients as opposed to chronic bronchitis.

Chronic bronchitis is defined clinically as chronic cough with sputum production on most days for a minimum of three consecutive months in a year for at least two years. Patients with pure emphysema, on the other hand, may present with exertional dyspnea as the only symptom. Although chronic bronchitis and emphysema are often discussed separately, it is uncommon to see these diseases in pure forms. More often than not they are present together, and it is difficult to separate them clinically. Therefore, they are best discussed under chronic obstructive lung disease. Certain differential features of chronic bronchitis and emphysema are given in Table 1.

In the aging population, the diagnosis of chronic obstructive lung disease is often made inappropriately in an effort to explain a patient's dyspnea. The gradual increase in anteroposterior diameter of the chest and dilatation of alveoli that accompany aging result in a superficial resemblance to emphysema: in fact, the ill-advised misnomer "senile emphysema" has been applied to these changes. If one requires strict criteria for the diagnosis of COLD, this mistake can be avoided. Clinical history may vary, but physical signs are very helpful. Percussion of the posterior wall of the chest should reveal significant limitation of diaphragmatic excursions in virtually all symptomatic patients with COLD, and either wheezing or decrease in air entry is generally quite evident.

COLD is a chronic, progressive disease in which the pathologic process greatly accelerates age-related loss of pulmonary function. For example, the mean loss of FEV_1 in these patients is 80 ml per year as opposed to 28 ml per year in normal subjects. There is little that can be done to check this progressive deterioration once the disease is well-established. However, adjunctive therapy[13] and patient education can reduce the need for hospitalization and improve the quality of life.

Control of Infection

Infections, whether viral or bacterial, worsen symptoms and may even precipitate acute respiratory failure. Respiratory infections, therefore, must be treated early and vigorously until maximal benefit is obtained. Undoubtedly most of the infections are viral, but bacterial overgrowth is quite frequent. Since the most common pathogenetic organisms are D. pneumococcus and H. influenza, ampicillin, tetracycline, and erythromycin are commonly used. The patient is advised to start the antibiotic at home whenever his sputum increases in quantity or becomes tenacious or purulent. The antibiotic should be continued for at least 7 days. Influenza polyvalent vaccine should be given each fall.

Bronchodilatation

Many bronchodilating preparations are available, and the choice depends on the patient's acceptance. Ephedrine preparations should be avoided because they may cause difficulty in urination in elderly patients with prostatic enlargement, arrhythmia, and insomnia. Newer bronchodilators, such as terbutaline sulfate, by their selective stimulation of B_2 adrenergic receptors, provide good bronchodilation with minimal effect on the cardiovascular system.

For obvious reasons steroids should not be used routinely in the elderly with chronic obstructive lung disease. However, patients with asthmatic bronchitis and some with chronic bronchitis may improve dramatically with steroid therapy. Identification of these patients is important. A "steroid trial" of one week at a daily dose of 30 to 40 mg of prednisone is worth considering for those respiratory cripples who show some response to an inhaled bronchodilator. Eosinophilia or eosinophils in the sputum in such patients are another indication for a "steroid trial." All patients must be evaluated carefully with objective data before embarking on long-term steroid therapy.

Hydration and Electrolyte Abnormalities

It is important for patients with chronic obstructive lung disease to be well-hydrated so that bronchial secretions do not become dry and inspissated. Elderly patients are also more likely to become dehydrated than their younger counterparts for several reasons, including increased use of diuretics for concomitant heart failure and impaired thirst mechanism secondary to organic brain damage. The clinician must use a balanced approach in treating a patient with COLD and heart failure. Diuretics are useful in the latter, but impair clearance of bronchial secretions. Therefore, it is better not to use them for minimal peripheral edema unless left heart failure is also present.

Diuretics have the added disadvantages of causing hypokalemic and hypochloremic metabolic alkalosis. Metabolic alkalosis may precipitate arrhythmias, reduce cerebral blood flow in an already compromised cerebral vascular system, and perhaps decrease respiratory center drive. Hypokalemic, hypochloremic alkalosis can be avoided by adequate supplements, usually given as a potassium chloride solution.

Bronchial Hygiene

The most efficient way to keep airways clear is to liquefy sputum with good hydration and inhaled moisture. The patient should be taught the process of inhaling a bronchodilator delivered by hand nebulizer, followed by postural drainage and voluntary effective coughing. This procedure should be carried out three or four times a day in a patient with severe disease. The value of home use of intermittent positive pressure breathing (IPPB) machines, for immediate or long term clinical improvement, is controversial.

Continuous Oxygen Therapy[6]

Hypoxemia is one of the hallmarks of COLD and presents with protean manifestations. Continuous oxygen therapy not only relieves pulmonary hypertension but also improves exercise tolerance and mental function and produces a general sense of well being. Continuous oxygen therapy has been established as a practical form of treatment at home. Arterial oxygen saturation of about 80 per cent is easily maintained with a nasal cannula at a flow rate of 1 to 2 liters per minute. Oxygen should be given continuously for 24 hours or at least 15 hours a day to have any demonstrable effect. Even when continuous oxygen therapy is impractical or unacceptable, its use during sleeping hours can alleviate insomnia, nightmares, and headache. During outdoor activities, a 9.5 tb Linde oxygen walker system provides portable insulated liquid oxygen for 4 hours at 2 liters per minute. Continuous oxygen therapy is expensive, but it has considerably reduced hospital admissions and the eventual cost of medical care to the patients and the community.

Physical Therapy

The immediate goal of physical therapy is to alleviate symptoms and to increase the patient's mobility. Breathing retraining and reconditioning exercises enable the patient to utilize his limited pulmonary functions to their maximum.

Normally in quiet breathing, the diaphragm is responsible for about 65 per cent of pulmonary ventilation, while the intercostal muscles are responsible for the remaining 35 per cent. In emphysema, the diaphragm is depressed because of increased lung volume and contributes only 30 per cent of the effort. This results in laborious breathing and considerable increase in the oxygen cost of breathing. To utilize the diaphragm maximally, the patient is taught to inspire rapidly with the abdomen moving outward, and then to expire slowly through pursed lips, with the abdominal muscles moving inward. Pursed-lip breathing prevents early airways closure. With practice, this procedure has been shown to decrease dyspnea and, to some degree, improve arterial blood gas levels.

With a regular exercise training program, physical endurance can be substantially improved without any improvement of pulmonary functions. This can be accomplished with simple daily walking exercises or stationary bicycle exercise, gradually increasing to maximal tolerance without exhaustion. Improved endurance improves the patient's general outlook and sense of well-being.

ACUTE RESPIRATORY FAILURE

It is not uncommon for patients with COLD to seek medical help for the first time during an episode of acute respiratory failure. In the course of their chronic disease, many patients have frequent acute exacerbations that may result in increasing hypoxia and hypercapnia, leading to

Table 2. *Differentiation of Acute Pulmonary Edema and Acute Respiratory Failure due to COLD*

	ACUTE PULMONARY EDEMA "CARDIAC ASTHMA"	ACUTE RESPIRATORY FAILURE DUE TO COLD
History	Hypertension, anginal syndrome, old myocardial infarction, valvular disease.	Smoking, cough, and sputum production of long duration.
Onset	Sudden or shorter duration.	Longer duration of symptoms.
Symptoms	Shortness of breath, history of nocturnal dyspnea.	Shortness of breath with wheeze. Insomnia and drowsiness during day. Nocturnal dyspnea relieved by cough and expectoration.
Signs	Pulse is rapid and thready. Hypotension to hypertension. Skin cold and clammy. Chest: Predominantly bubbling rales, occasional wheeze. Heart: S_3 gallop. Murmur may be present.	Bounding pulse. Normotensive. Cyanosed but warm extremities. Predominantly wheeze, occasional rales. Gallop uncommon.

Chest x-ray	Left ventricular enlargement. Kerley's B line. Butterfly type alveolar infiltration.	Clear lung fields.
Electrocardiogram	Left ventricular hypertrophy. Evidence of old or new myocardial infarction. Arrhythmias of ventricular origin. Conduction defects.	"P" pulmonale. Right ventricular hypertrophy. Arrhythmias of atrial origin.
Sputum	Frothy, white, or pink.	Purulent, thick sputum. Organism and pus cells on gram stain. Occasionally eosinophils on Wright's stain.
Hematocrit	Normal	Elevated
Pulmonary function abnormalities	Restrictive type; i.e., low FVC but normal FEV_1/FVC ratio	Obstructive type; i.e., low FVC but also very low FEV_1/FVC ratio.
Arterial blood gases	Metabolic acidosis associated with respiratory alkalosis or acidosis.	Respiratory acidosis High Pco_2
Electrolytes	Low CO_2 content.	Low chloride and high CO_2 content

somnolence, coma, cardiac arrhythmias, and death. The mortality rate from acute respiratory failure is high and rises from 37 per cent at age 40 to virtually 100 per cent at age 85. Two-thirds of the survivors die within 2½ years of the episode.[4]

It is often difficult to distinguish acute respiratory failure from pulmonary edema, and in fact, respiratory failure in a patient with cardiac disease may precipitate acute left ventricular failure. An accurate diagnosis is important because therapy for these two conditions is quite different. Morphine, for example, is useful in pulmonary edema, but may lead to apnea in a patient with respiratory failure. Certain characteristic differences between these two conditions are summarized in Table 2. In most cases, however, only some of these findings are present, and occasionally, differentiation is impossible without cardiac catheterization.

Management of Acute Respiratory Failure due to COLD[7]

Once the diagnosis is made, two basic principles are followed: correction of hypoxemia, and reduction of arterial P_{CO_2} level.

When the patient is alert and has a normal or modestly elevated P_{CO_2} and hypoxemia, a controlled concentration of oxygen can be given by any method that is convenient and comfortable to the patient. If the P_{CO_2} is moderately elevated on admission, there is a serious risk of developing severe hypercapnia, and oxygen delivery must be strictly monitored. Generally an oxygen saturation of about 80 per cent is adequate for tissue oxygenation, and one should not risk severe hypercapnia and respiratory acidosis by raising the saturation further. Desired oxygen saturation can usually be achieved with a 24 per cent ventimask or nasal cannula with a flow rate of 1 to 2 liters per minute. When the desired oxygen saturation is not achieved, the inspired oxygen concentration should be gradually increased, and arterial blood gases should be measured in 15 to 20 minutes. During this stage, the patient is encouraged to cough effectively and expectorate. The amount, color, and viscosity of sputum are charted. The patient's mentation and arterial P_{CO_2} must be closely watched.

If drowsiness develops or hypercapnia increases, an intubation set and respirator should be kept available. Intensive physiotherapy, supplemented with nasotracheal suctioning, should be carried out more frequently. If improvement is not seen quickly, arrangements for intubation must be made.

After oral or nasal endotracheal intubation, artificial ventilation is begun and vigorous tracheal toilet should be continued. The endotracheal tube may be kept in place safely for several days. Tracheostomy should be performed electively in the operating room if artificial ventilation is required for a longer time. Supportive therapy is maintained until the patient can ventilate adequately by himself. In the recovery phase, the patient is usually weaned off the respirator slowly.

Sedatives and tranquilizers should never be used unless the patient receives mechanical ventilatory support. At present, there is no safe and effective respiratory stimulant available.

In addition to providing ventilatory assistance, one must control the factors leading to acute respiratory failure: infection, inspissated secretions, and bronchospasm. Effective humidification of the airways is essential to overcome inspissated secretions, and systemic hydration is helpful if the patient is not in heart failure. Fluid and electrolyte abnormalities must be corrected. Aminophylline is the preferred bronchodilator and may be given by continuous intravenous infusion in a dose as high as 0.90 mg per kg of body weight per hour after a loading dose of 6 mg per kg of body weight infused in 10 to 20 minutes. Higher doses may cause death from central nervous system toxicity. As the elderly are more prone to develop arrhythmias with aminophylline, continuous electrocardiographic monitoring is important.

PNEUMONIA

Despite the availability of many potent antibiotics, pneumonia remains one of the leading causes of death in the United States. One major reason is its high incidence in the elderly, who tolerate its effects more poorly than younger individuals. There are probably many reasons for this increased susceptibility, including the presence of degenerative diseases such as arteriosclerotic heart disease, cerebrovascular accidents, chronic obstructive lung disease, and uremia, all of which predispose one to respiratory infection. Aspiration from dysphagia, whether from cerebrovascular disease, Parkinsonism, or a local cause, is one of the most common precipitating factors.

Even healthy elderly people often have poor muscle tone, which impairs their ability to cough up tracheobronchial secretions, and these retained secretions and foreign particles enhance bacterial growth. If they smoke, their ciliary action in the bronchi and bronchioles may be impaired so that particles trapped on mucus are not carried upward to the pharynx. The effect of aging per se on the cilia is not known.

Altered immunity may be another factor predisposing to pneumonia. Secretory immunoglobulin (IGA) of the nasal and respiratory mucosal surfaces, a major deterrent to viral infection, is decreased with advancing age. These local antibodies prevent colonization of mucus membranes and neutralize viruses. Once viral infection is established in the respiratory tract, it inhibits the phagocytic activity of alveolar macrophages, the last line of defense against pneumonia. However, the significance of decreased secretory IGA in the elderly is not clear because intranasal inoculation of inactivated influenza virus in these people causes an adequate increase in local IGA titer. Poor serum antibody response to antigen and impaired cellular immunity may also decrease resistance to infection.

Clinical Features

The typical clinical picture of pneumonia is often incompletely expressed in elderly patients. The onset may be insidious with malaise and mental confusion as the only early signs. Pneumonia in patients past 60 frequently does not result in copious, purulent sputum, and coughing may be mild and ineffectual. Sometimes pneumonia first manifests itself through dramatic complications such as congestive heart failure, acute respiratory failure in COLD patients and septic shock. In other cases, typical symptoms of pneumonia appear abruptly and overwhelm the patient in a day or two.

Fever may be absent or delayed and mild, especially in patients with gram-negative pneumonia, in shock, or taking steroids. There is usually tachycardia and tachypnea but rarely pleuritic pain. Initially chest dullness, bronchial breathing and even rales may be absent. Rales can often be evoked by having the patient hyperventilate and are sometimes the only findings in the lungs throughout the course of the illness. Rapid and shallow breathing may lead to mucus plugging, and migratory rales may be heard even in areas of the lung uninvolved with pneumonia.

Blood cultures should be obtained in all suspected cases. A positive culture is found in 30 per cent of patients with Pneumococcal pneumonia. Although the latter is the most common bacterial pneumonia, in cases acquired in the hospital, a Staphylococcal or gram-negative etiology should be seriously considered. Gram-negative pneumonia is more common in elderly people with debilitating diseases.

The chest x-ray is often rather undramatic in the elderly. Lobar consolidation with an air-bronchogram is usually not seen. Oswald[15] found that with increasing age, more cases of pneumonia appear with mottled rather than homogeneous consolidation, especially in patients with emphysema. Incomplete consolidation must be differentiated from necrotizing bacterial pneumonia and pneumonia around a tuberculous cavity.

The localization of the infiltrate in gram-negative pneumonia is of some diagnostic value. Bacteroides, E. coli, and Pseudomonas aeruginosa produce predominantly lower lobe pneumonia, frequently with large empyemas. Proteus and Klebsiella-Aerobacter infections, on the other hand, usually invade the upper lobes with more dense infiltrates, and rarely cavitate or form empyemas.[11]

Treatment

On the basis of the gram-stain and the clinical picture, specific antibiotic therapy must be instituted immediately. Unfortunately, elderly people do not respond as well as younger patients even with correct antibiotic therapy, and their mortality rate is higher. Delayed resolution of pneumonia, defined as incomplete clearing of the chest x-ray density after four weeks of adequate therapy, is four times more common in patients over age 50 as in those under 50. Although most patients with gram-positive cocci on smear have Pneumococcal pneumonia, one must consider treating for Staphylococcal pneumonia with a penicillinase-resistant penicillin if the patient is overwhelmingly ill, acquired the infection in the hospital, or has multiple roentgenologic lesions.

Gram-negative pneumonias are treated with a combination of an aminoglycoside antibiotic with ampicillin or a cephalosporin. Because of nephrotoxic and ototoxic effects of the aminoglycosides and variations in achieved blood levels, monitoring of their blood levels is advisable. If this is not possible, dosage must be based on body weight, and interval between doses, on creatinine clearance.

Other important measures include systemic hydration to liquefy sputum, encouragement of cough, nasotracheal suction when necessary, and cupping and postural drainage. Sputum-liquefying agents are of doubtful value. Sedatives and cough suppressants should be avoided. Blood gases should be determined, and oxygen administered if arterial oxygen saturation is below 90 per cent. Early mobilization and avoidance of constipation and straining are important in order to minimize the likelihood of pulmonary embolism.

ASPIRATION PNEUMONIA

Aspiration of gastric contents and oropharyngeal secretions is common among the elderly but seldom produces any clinical symptoms. The likelihood of ill effects from aspiration depends on the frequency, volume, and character of the aspirate. "Aspiration syndromes"[5] are best described in three forms even though the clinical picture is often mixed. They involve aspiration of solid particles, gastric acid contents, and pathogenic bacteria.

Aspiration of Solid Particles

Aspiration of large solid food particles with obstruction of the larynx or trachea may cause sudden respiratory distress, violent cough, cyanosis, and death. This often occurs in elderly patients, particularly among the debilitated, those with neuromuscular disease, and eehaving undergone recent endotracheal intubation. Quite often this aspiration mimics acute myocardial infarction or pulmonary emboli. The presence of aphonia is a clue to aspiration of food particles. Quick diagnosis is imperative to save the patient's life. Smaller food particles that reach one of the bronchi may cause severe dyspnea and wheezing, simulating bronchial asthma. Secondary bacterial infection following aspiration of solid particles is common. Management of the aspiration includes prompt removal of solid particles and the administration of an antibiotic, usually penicillin.

Aspiration of Gastric Acid

Aspiration of gastric acid, so called "Mendelson's syndrome," is a serious disorder with a high mortality rate. For the syndrome to develop, the patient has to aspirate 50 to 300 ml of gastric acid with a pH less than 2.5. Clinical signs and symptoms, usually developing between 2 and 12 hours after aspiration, are characterized by acute dyspnea, cough with frothing sputum, tachycardia, cyanosis, rales, sometimes bronchospasm, and often hypotension. Chest x-ray reveals soft, mottled densities in one or both lower lung fields. The roentgenologic findings resemble pulmonary edema except for the absence of pulmonary venous congestion and cardiomegaly. The measurement of arterial blood gases is mandatory in this condition. Severe hypoxia with normal or low P_{CO_2} is a common finding. Hypoxia in this condition is due to atelectasis, edema, and alveolar hemorrhage.

The management of Mendelson's syndrome consists of the correction of hypoxia, which may require intubation and mechanical ventilation with or without positive end-expiratory pressure. Tracheal toilet to maintain a clear airway is necessary. Corticosteroids may abort a full blown picture when started within 4 hours of aspiration of gastric acid contents, but the size of the dose remains a subject of controversy, varying from 1 gm of hydrocortisone to 1 gm of methyl prednisone daily for 1 to 2 days. The administration of penicillin is usually adequate to prevent secondary infection.

Aspiration of Pathogenic Bacteria

Bacterial pneumonia may follow Mendelson's syndrome, but it more commonly occurs following recurrent aspirations of small amounts of gastric contents and oropharyngeal secretions. This repeated aspiration is usually associated with specific predisposing conditions such as a reduced level of consciousness from cerebrovascular accident; drug overdose with consequent compromise of glottic closure and cough reflex; dysphagia from neurologic or esophageal disorders; and mechanical disruption of the "cardiac sphincter" due to nasogastric tube feedings. The nasogastric tube also enhances colonization of gram-negative bacteria.

The clinical picture is often nonspecific with low grade fever, unproductive cough, and gradual deterioration of the patient. The posterior segment of the upper lobe and superior segment of the lower lobe, the two most dependent segments when the patient is recumbent, are commonly involved. Organisms are most often multiple, including Pneumococcus, anaerobic Streptococci, and Bacteroides in community-acquired aspiration. In hospitalized patients, E. coli, Pseudomonas, and Staphylococcus aureus should be considered.

Penicillin G is the drug of choice in community-acquired aspiration pneumonia, but in hospital-acquired disease, a penicillinase-resistant penicillin and gentamycin may be required until the sputum culture and sensitivity results are available. Anaerobic cultures for Bacteroides are required in nonresponsive cases and clindamycin is the drug of choice for Bacteroides fragilis.

Lipoid Pneumonia

Lipoid pneumonia is a foreign body reaction to mineral oil. The elderly are frequent users of laxatives and nasal medications that contain mineral oil and also are more likely to aspirate it. Repeated exposure of the lungs to mineral oil evokes an insidious process that leads to a mass of fibrous tissue replacing normal lung, enclosing pools of oil and surrounded by giant cells, lymphocytes, and plasma cells. Local arteries are completely thrombosed. Chest x-ray reveals either homogeneous consolidation of one or more lobes or a peripheral circumscribed mass. Lipoid pneumonia rarely causes symptoms and requires no therapy. Its major importance lies in distinguishing it from bronchogenic carcinoma. A careful history and microscopic examination of fresh wet sputum are necessary for proper diagnosis. The sputum smear stained with Sudan dye shows engorged alveolar macrophages with foamy cytoplasm and orange-brown vacuoles.

TUBERCULOSIS

At the beginning of the twentieth century, tuberculosis was the leading cause of death in the United States, as well as in the world. The advent of chemotherapy has brought a dramatic decline of mortality and a steady decline in the number of new cases reported in developed countries. Yet 30,000 new cases are still reported each year in the United States and 12 to 15 million positive tuberculin reactors (infected persons) constitute a considerable potential source of new cases of tuberculosis. The age range for active tuberculosis has shifted dramatically in recent years. Now 85 per cent of new cases develop in people over 25 years of age and half in patients past 45. Two thirds of new cases are in males.[9] Elderly subjects handle the tubercle bacillus more poorly than young individuals. Cavitary and liquefied lesions, miliary tuberculosis, tuberculous meningitis, and other extrapulmonary forms are more common in the latter decades.

Active tuberculosis late in life is usually the result of reactivation of pre-existing "inactive" lesions acquired earlier in life. This reactivation of dormant infection may occur because of a decline in host resistance with advanced age. The allergic response to tuberculous bacilli, as measured by skin tests, declines after age 50, perhaps because of a failure of the reticuloendothelial system to provide sufficiently sensitized lymphocytes. In addition, poor housing, inadequate diet, and degenerative diseases such as chronic obstructive lung disease, diabetes mellitus, cancer, and blood dyscrasias may contribute to activation of tuberculosis.

Older subjects tend to have fewer and less marked symptoms than younger people. Indeed, the progress of the disease is often so slow that months may elapse before it is correctly diagnosed. Symptoms such as cough, sputum, and dyspnea are nonspecific. Even in miliary tuberculosis, the weakness, anorexia, fatigue, weight loss, and intermittent fever are often insidious. Even a normal temperature does not exclude the possibility of tuberculosis. Physical examination often contributes little to the diagnosis. Consequently, tuberculosis in the elderly is often undiagnosed until a relatively late stage.

Diagnosis

The diagnosis of pulmonary tuberculosis is made on the basis of skin testing, chest x-ray, and sputum examination. Demonstration of an allergic response to tuberculous protein is best accomplished by intradermal injection of intermediate strength PPD (5 tuberculin units). This tuberculin skin test may be negative in patients with active tuberculosis who are old or chronically ill, and even a second strength PPD (250 unit) may be negative in very debilitated patients and in those with

Table 3. *Toxicities of Antituberculous Drugs*

DRUG	TOXICITY	SYMPTOMS AND SIGNS OF TOXICITY	PROGNOSIS
INH (isoniazid)	Hepatitis	Anorexia and jaundice	Reversible, if recognized early; potentially fatal
	Peripheral neuropathy	Burning feet and sensory loss	Reversible and preventable with pyridoxine administration
Streptomycin	Vestibular and cochlear damage	Tinnitus, vertigo and hearing loss	Reversible in early stages
Ethambutol	Retrobulbar neuritis	Decreased visual acuity and green color blindness	Reversible in early stages; potential cause of blindness
Rifampin	Allergic thrombocytopenia when used intermittently	Purpura	Reversible
	Flu-like syndrome	Malaise	Reversible
	Cholestatic jaundice	Jaundice	Reversible

acute miliary tuberculosis. With proper therapy, conversion of a negative to a positive skin test as the patient improves is of great diagnostic value.

In the active stage of tuberculosis, some form of abnormality is seen on chest x-ray except in miliary tuberculosis, where the nodules may be too small and ill-defined to visualize early in the course. Difficulty in interpretation lies in predicting whether a roentgenologic lesion is active. Even a partially calcified lesion may be clinically significant.

Sputum, spontaneous or induced, should be examined by smear and culture. When sputum is not available, a fasting, morning gastric aspirate should be examined by culture for M. tuberculosis. When miliary tuberculosis is suspected, a morning specimen of urine for culture and bone marrow aspirate and liver biopsy for demonstration of granuloma and tubercle bacilli should be obtained. In the elderly, a lumbar puncture is also necessary because tuberculous meningitis may be quite occult in the early stages.

Treatment

The mortality and morbidity of tuberculosis are higher in older subjects. D'espo and Bernstein[8] noted that 95 per cent of the younger group receiving their first course of chemotherapy had a satisfactory clinical result, while only 83 per cent of the group over 50 years responded as well. Similarly, the results of retreatment were slightly inferior in the older group. Successful treatment of pulmonary tuberculosis in older subjects depends on early diagnosis, proper chemotherapy, and proper management of co-existing disease.

The therapy of active tuberculosis should always include two or more drugs. Two effective regimens are: (1) isoniazid (INH) 300 mg per day and rifampin, 600 mg per day; and (2) INH, 300 mg per day and ethambutal, 25 mg per kg per day for 2 to 3 months, followed by 15 mg per kg per day. Streptomycin, ½ gm daily, is added only in the far advanced stage of the disease. Other potentially toxic drugs are reserved for treatment of cases with resistant organisms. Drug therapy should be continued for 2 years except for parenteral drugs, which are usually discontinued after 3 to 6 months. Recent experience suggests that duration of therapy may be shortened to 9 months when two bactericidal drugs (INH and rifampin) are employed. The toxicity of the major antituberculous drugs is summarized in Table 3.

Preventive Therapy

It has been clearly shown that tuberculosis can often be prevented by reducing the bacterial population in the "healed" lesion with preventive therapy (chemoprophylaxis). A bactericidal drug, isoniazid (INH), in a single dose of 300 mg per day for 12 months, is effective. This form of therapy is not free of side effects, the most common being the elevation of serum glutamic oxalacetic transaminase (SGOT) and other liver enzymes, especially during the first 2 months of therapy.[19] This abnormality may occur in 40 per cent of treated patients. Its frequency increases with age, especially among Caucasians. Fortunately, it tends to subside completely even when INH is continued.

In occasional instances, a syndrome clinically, biochemically, and histologically indistinguishable from viral hepatitis may develop and lead to progressive and even fatal liver damage. This is rare in patients under 20 years of age, but in patients over 50 years of age, INH hepatotoxicity may occur in 2 to 3 per cent of subjects. At present, there is no definite method of predicting which patients will suffer hepatotoxicity but it appears that liver toxicity may be caused by chemically reactive metabolites of INH.[19] One such product, acetyl hydrazine, is converted into a potent acylating agent that produces liver necrosis. This suggests that those patients whose livers acetylate INH metabolites rapidly may be at greater risk. It is possible that this information will aid in the development of a screening test for susceptibility to INH-hepatitis.

In general, the likelihood of developing active tuberculosis in the tuberculin-reactive elderly, except for certain high risk groups, is less than that of developing INH-induced hepatitis. Its routine use is not justified at this moment. INH preventive therapy should be reserved for the following patients:[1]

(1) those with a positive tuberculin test reaction and an abnormal chest x-ray, where the reactivation rate has been observed to range between 1.0 and 4.5 per cent per year; (2) those with positive tuberculin test reactions and a negative chest x-ray, but with increased risk factors such as (a) prolonged therapy with adrenocorticosteroids, (b) immunosuppressive therapy, (c) some hematologic diseases such as Hodgkin's disease or leukemia, (d) diabetes mellitus, (e) postgastrectomy state, (f) malnutrition, (g) alcoholism, (h) silicosis.

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Pulmonary Disease Division
Coney Island Hospital
2601 Ocean Parkway
Brooklyn, New York 11235

Interpretation of Gastrointestinal Symptoms in the Elderly

*Francis U. Steinheber, M.D.**

In dealing with the elderly patient, it is often difficult to differentiate between insignificant, functional gastrointestinal problems that can be treated symptomatically and others that may be harbingers of serious underlying disease. This article focuses on a number of these commonly encountered gastrointestinal symptoms in the elderly. Detailed reviews on the physiologic consequences of aging can be found elsewhere.[3,14]

DIFFICULTY IN SWALLOWING AND RELATED SYMPTOMS

Elderly patients who complain of difficulty in swallowing must be thoroughly investigated. The previously accepted notion of a specific motility defect related to aging, implied by the term presbyesophagus, has been recently questioned. From their studies on men over the age of 70, Hollis and Castell concluded that while a marked decline in the amplitude of propulsive contractions may occur with age, the remainder of the peristaltic complex and the incidence of abnormal spontaneous contractions are similar to younger control patients.[19]

Recognition of Esophageal Disease

In the elderly, problems of deglutition may be overshadowed by their clinical consequences. Patients often present with pulmonary symptoms secondary to chronic aspiration. Recurrent pneumonia or bronchiectasis may be the first clue to esophageal disease. Similarly malaise, weight loss, and low grade fever associated with a lung abscess may precede for a long period the detection of a swallowing difficulty.

It is not difficult to ascribe symptoms of esophageal disease to other causes when dealing with the elderly. For example, ill-fitting dentures frequently force patients to decrease their intake of solid food. The resulting difficulty in mastication is one of the chief reasons for weight loss and poor nutrition in older people. Yet the slow, insidious transition to soft food is also the identifying characteristic of esophageal obstruction, which may be overlooked if the patient cannot provide a good history.

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* Chief of Gastroenterology Division, Coney Island Hospital; Instructor in Clinical Medicine, New York University School of Medicine

At times it is difficult to distinguish pain of esophageal disease from heart disease in the elderly. As a general rule, pain associated with swallowing indicates an organic esophageal lesion. However, on rare occasions, disease extrinsic to the esophagus such as pericarditis may produce this kind of pain. More often pain bears no direct relationship to swallowing. In reflux esophagitis, the substernal discomfort is often identical with angina pectoris. Although the former is more intimately related to meals and recumbency and the latter to exertion, the distinction tends to blur in the elderly. Perfusion of dilute acid into the esophagus is often helpful in differential diagnosis. In addition, associated motility problems of varying degrees may cause chest discomfort without clearly definable characteristics. Not infrequently, both coronary artery disease and hiatus hernia with reflux are present, and it may be difficult or impossible to determine how much each is contributing to the patient's symptoms. Esophageal reflux may also mimic congestive heart failure by causing paroxysms of cough with dyspnea that interrupt sleep. Asthmatic attacks, hemoptysis, intractable cough, and chronic pulmonary insufficiency may result from this process. Reflux has even been held responsible for hoarseness, neck pain, and otalgia.

Differential Diagnosis of Esophageal Disease

The causes of dysphagia do not change substantially with age,[28] but greater priority must be given to certain diagnoses. A history of intermittent rather than progressive symptoms, inability to handle liquids as well as solids, and increased distress with very hot or very cold foods are all characteristic of a motility disorder. However, symptomatic motility disorders are not common in the elderly even though an esophagram often shows a "corkscrew" appearance. Classic achalasia is seldom encountered in the elderly. For this reason, it is imperative to look carefully for an obstructive lesion whenever barium is unable to pass easily beyond the region of the lower esophageal sphincter on x-ray.

Carcinoma of the esophagus is the most common cause of progressive dysphagia in the elderly, and every effort must be made to exclude this possibility. Although a long history of heartburn, typical postural symptoms, and slow evolution of dysphagia favor the diagnosis of a benign peptic stricture, this diagnosis should not be accepted until thorough investigation has ruled out malignant obstruction. Similarly, the known presence of a hiatus hernia for many years offers no assurance that the stricture is benign. In fact, there is some evidence of an increased incidence of carcinoma of the cardioesophageal junction in patients with longstanding hiatus hernia.

A mid-esophageal stricture in the absence of the ingestion of caustic substances generally arouses suspicion of Barrett's esophagus (heterotopic gastric epithelium). Recent reports indicating the premalignant nature of this columnar epithelium emphasize the need for close follow-up of patients with known Barrett's esophagus. To date, however, development of cancer in a Barrett's esophagus has not been reported in patients over the age of 75.[8] Metastatic cancer to the esophagus or extrinsic invasion by a locally infiltrating malignancy in a mid-esophageal location may resemble a Barrett's stricture. The most common neoplasms that secondarily involve the esophagus are bronchogenic and breast cancer. While the primary tumor is usually evident at the time of esophageal involvement, on occasion dysphagia may be the initial symptom.

While some patients with dysphagia may accurately sense the level of obstruction of a lower esophageal lesion, it is more common to falsely localize the site to another area such as the upper esophagus or even the pharynx. On the other hand, obstruction at an oropharyngeal site is never referred to the lower esophageal area. An approximate but more reliable guide to the level of obstruction is the time in seconds from the start of swallowing to the point when the sense of sticking occurs. Difficulty in initiating swallowing, nasal regurgitation of food, or disproportionate difficulty in swallowing liquids suggests an oropharyngeal problem.

A Zenker's diverticulum is a common cause of upper esophageal symptoms, particularly in elderly men. Strictly speaking, this is a pre-esophageal problem since the pouch arises from the posterior wall of the hypopharynx. Because of associated cricopharyngeal motor dysfunction, the patient may note difficulty in passing food beyond the pharynx and experience a choking sensation. As the disease progresses, the enlarging pouch compresses the upper esophagus while retained debris leads to nocturnal regurgitation of undigested food, aspiration pneumonia, halitosis, and even gurgling sensations in the neck.

Cervical esophageal and hypopharyngeal webs may also cause upper esophageal dysphagia. With new techniques, it is now possible to demonstrate unsuspected webs in about 5 per cent of asymptomatic patients.[25] Most of these patients do not have iron deficiency anemia. Despite the frequent lack of association of post-cricoid webs, upper esophageal dysphagia, and iron deficiency anemia, it seems appropriate to designate the combination of these findings as Plummer-Vinson syndrome,[7] since the term does identify a clinically distinct group of patients, most of whom are women, with a significant risk of developing carcinoma of the hypopharynx. In this regard, it seems more than coincidental that more than 90 per cent of all cases of cancer of the hypopharynx occur in women, half of whom have a long history of dysphagia.

Disturbances in deglutition are common in patients with cerebrovascular disease (bulbar or pseudobulbar palsy). In rare instances, oropharyngeal dysphagia is the only sign of a stroke in the basilar artery distribution. Sudden onset of dysphagia associated with other neurologic signs of brain stem disease, however subtle, should alert one to this diagnosis.

Recent manometric data have tended to minimize the role of hiatus hernia in producing esophageal symptoms. A number of studies indicate that the lower esophageal sphincter is crucial in preventing reflux of gastric contents into the esophagus and that the competence of this sphincter is unrelated to the presence or absence of a hernia. This change in emphasis has had the salutary effect of restraining the tendency to ascribe all upper gastrointestinal symptomatology to a hiatus hernia, especially since the latter seems to be an invariable accompaniment of advancing age.[34] With the increasing tendency to minimize the importance of hiatus hernia, however, it is easy to lose sight of problems which are a direct consequence of the displaced stomach such as occult or overt bleeding from the hernial pouch.

In much the same way, the special problems of the paraesophageal hernia have become increasingly neglected. In this latter case, the hernia itself occasionally results in prominent symptoms such as substernal discomfort after meals and difficulty in swallowing. More importantly, it is particularly prone to develop incarceration and acute obstruction.[18] This complication may appear dramatically with the acute or subacute onset of severe upper abdominal or substernal pain associated with retching and inability to regurgitate gastric contents. These symptoms, coupled with an inability to pass a nasogastric tube, have been regarded as diagnostic of a volvulus of the stomach, which is the mechanism involved in obstructing paraesophageal hernias. Since incarceration has developed in up to a third of patients with paraesophageal hernias, they do constitute an ever present threat. Patients have often been told previously of the presence of such a hernia which they may describe as "upside-down stomach."

No discussion of dysphagia in the elderly would be complete without reference to symptoms caused by extrinsic compression. While esophageal compression by aberrant vessels (arteria lusoria), an uncoiled aorta and its branches, and even enlarged cardiac structures have all been described, these situations are quite uncommon. Even less common are those instances of compression by cervical osteophytes. These kinds of obstruction should only be a diagnosis of last resort after all other possible causes have been eliminated.

ALTERATION OF BOWEL HABITS

Constipation

There is little supporting evidence for the generally held view that constipation is a natural consequence of aging. Most surveys indicate that 80 to 90 per cent of patients over age 60 have one or more bowel movements daily. It is true, however, that in this age group, undue preoccupation with bowel habits and mistaken ideas of the value of cathartics lead to excessive use of laxatives. Half of this population, especially women, use some laxatives. With declining activity, changes in diet necessitated by poor dentition, or medical regimens as well as increasing use of drugs, some alteration of bowel habits is to be expected. In evaluation of a patient with complaints related to bowel function, it is first necessary to establish the patient's definition of "normal" and precisely the manner in which his bowel habits have changed. If there has been a distinct progressive change in the number of movements per day or a substantial change in laxative requirements, further investigation is necessary even if there are no other obvious symptoms such as pain, bleeding, or loss of weight.

Whenever an elderly patient complains of a decrease in bowel motions, the possibility of cancer of the colon becomes the immediate concern. Contrary to popular belief, constipation occurs in less than one third of cases of cancer of the colon and is less common than diarrhea. Moreover, right-sided lesions increase in frequency with age, although the left colon remains the predominant site of involvement. Almost one third of colonic cancers in patients over 80 years of age occur on the right side.[1] Lesions in this location are notoriously difficult to diagnose since less than half are associated with altered bowel habits.

The incidence of colonic diverticulosis increases directly with age and diverticula can be found in up to 40 per cent of patients over the age of 70. Symptomatic diverticular disease is accompanied by constipation in over one third of the cases. Characteristically, however, periods of constipation or diarrhea are interspersed with periods of normal bowel behavior. On occasion one pattern may persist, most often constipation. Strictures secondary to diverticulitis may be radiologically indistinguishable from carcinoma of the colon. In one series, suspicion of cancer was the primary indication for surgery in a group of patients requiring operation for non-acute diverticular disease.[4] In this group of patients it is surprisingly rare to find a history of previous diverticulitis or prolonged symptoms suggestive of diverticular disease.

Functional bowel disease is closely related to diverticular disease, but it is unusual for the classic irritable colon syndrome to appear for the first time after the age of 70. Patients in this age range with functional symptoms generally give a lengthy history of bowel irregularities with alternating diarrhea and constipation, although in later life one symptom may become increasingly dominant. On the other hand, vague complaints of abdominal pain, gaseousness and minor bowel irregularities are not uncommon. In this regard, the presence of ribbon-like stool reflects a motility disturbance rather than, as generally assumed, an organic narrowing. Progressive decrease in the caliber of the stool, however, suggests an organic lesion.

Seemingly minor causes of decreased bowel movements are apt to be overlooked. Often minimal rectal pain in a patient with an anal fissure may lead to voluntary withholding of the urge to defecate. A distended bladder resulting from an enlarged prostate may also cause increased difficulty in passing stool.

While constipation is generally an indication of colon pathology, it should be remembered that a decrease in the number of bowel movements may be an early sign of upper gastrointestinal or systemic disease. For example, constipation is a prominent accompanying complaint in some patients with pancreatic cancer. A number of systemic diseases may also manifest themselves as a primary bowel complaint. Although diarrhea is more widely recognized as a bowel disorder in diabetes mellitus, constipation is twice as common, rarely accompanied by a megasigmoid. Intractable constipation can be a troublesome problem in hypothyroidism and on occasion, may be the presenting manifestation. In hypercalcemic states, the symptoms of fatigue, nausea, and polyuria outweigh constipation, but occasionally the latter may be the main fixation of an elderly patient. Although classic intestinal angina is seldom seen, severe constipation may be a prominent symptom in the early phases of bowel ischemia, often to the extent of masquerading as a colonic neoplasm. Finally, elderly patients are avid consumers of many commercially available drugs, which can lead to constipation, for example, certain antacids or preparations containing iron.

Diarrhea

Clinical history is essential in evaluating a patient with diarrhea. This should include specific information about the mode of onset, accompanying systemic complaints such as weight loss and fever, local pain or tenesmus, and the character of the stool. It is equally important to note the frequency and pattern of bowel movements, especially nocturnal occurrence as well as the presence of blood or mucus on the stool. The patient should be closely questioned about travel, recent changes in diet, and the precise nature of any medications he may be taking.

Infectious diarrhea is characterized by the abrupt onset of diarrhea and fever. The diagnosis should be suspected if similar symptoms have occurred in close contacts or if the patient can recall a source of infection such as contaminated food. Likewise, certain drugs are known to precipitate diarrhea. Pseudomembranous colitis may follow use of certain antibiotics often prescribed for minor complaints. The most widely publicized antibiotic known to be associated with this problem at present is clindamycin. Many commercial antacids have laxative properties and may be used by a patient who vigorously denies the use of any "medicine."

Diarrhea of longer duration usually indicates a significant underlying problem. Rectosigmoid cancer remains the principal concern in an elderly patient, particularly if accompanied by pain, urgency, or blood in the stool. Half the patients with cancer in this location will develop diarrhea as a major symptom. Work-up always begins with a good rectal examination, which should enable one to diagnose a significant number of these tumors.

Inflammatory bowel disease is uncommon in the elderly and is frequently mistaken for other diseases considered more typical of old age. Nevertheless, a surprising 7 per cent of patients with ulcerative colitis develop their disease after age 65.[31] Clinical features in the elderly differ from those of younger patients. In many cases, the disease is limited to the rectosigmoid, and there are relatively few systemic complaints. The deceptively mild and unimpressive appearance of the patient's condition often belies significant pathologic changes. The onset of symptoms frequently follows significant emotional trauma and this relationship may aid in the diagnosis. After therapy, these patients have a better chance of remaining in remission.

Although the majority of cases of Crohn's disease appear in the second and third decade of life, there is also a striking propensity for disease with localized rectosigmoid involvement to develop in later decades, 70 per cent of cases being found in patients over age 45.[21] Disease limited to this area may be easily confused with diverticulitis, and in some instances the two problems may coexist.[23] The radiologic demonstration of long, longitudinal, intramural fistulous tracts or disease in another area of the colon or small bowel should suggest Crohn's disease, particularly if abnormal sigmoidoscopic changes or characteristic indolent anal fistulas are found. On occasion, ischemic or neoplastic strictures may mimic typical Crohn's disease. Where strictures are the only findings, full evaluation including colonoscopy is required.

In the elderly patient, the abrupt onset of abdominal pain and diarrhea is more likely to represent an episode of ischemic colitis than inflammatory bowel disease, and it is possible that many of the earlier published cases of the latter actually represent unrecognized ischemic disease. On initial examination it is often virtually impossible to distinguish the two entities clearly. Recent studies suggest that the rectosigmoid area is involved in more than half the cases of ischemic colitis.[33] Previous studies had indicated that the region of the splenic flexure is the most commonly involved area. Radiologic evidence of classical submucosal edema, called "thumbprinting," in the splenic flexure area or in another continuous area of the colon in a patient with apparent acute "proctosigmoiditis" should immediately suggest ischemic colitis. Acute onset or rapid resolution of ischemic colitis may be helpful in distinguishing it from inflammatory bowel disease. However, a certain number of patients with acute ischemic colitis may follow a fulminant course to gangrene or enter into a subacute phase with development of stricture. Chronic ischemic disease of the bowel or "intestinal angina," although initially presenting with constipation, evolves into a phase of severe diarrhea and weight loss. The diagnosis is suggested by a history of pain occurring 15 to 30 minutes after meals, often lasting several hours and leading to voluntary limitation of size of meals or even fear of eating. There is often a background of cardiovascular disease with a history of angina, myocardial infarction, stroke, or claudication. Evidence of peripheral arterial disease or an abdominal bruit is generally found on physical examination.

An uncommon but potentially serious dilemma may arise in cases of acute colitis proximal to an obstructing lesion of the colon. The colitis can easily be confused radiologically with ulcerative or ischemic colitis if careful attention is not directed to the area of obstruction. The obstructing event is usually a carcinoma, although rarely diverticular disease can be responsible.[12]

Mucoid loose stool mixed with blood often occurs in cases of villous adenoma, which may be mistaken for inflammatory bowel disease. While representing less than 10 per cent of all colonic polyps, villous adenomas increase in frequency with age and, in general, represent a more serious finding than adenomatous polyps. Sixty to 90 per cent are located within the rectosigmoid, but even when within easy reach of the examining finger, they may be missed because of their soft velvety nature. Moreover, the incidence of malignancy within the polyp ranges between 10 and 50 per cent depending on size, and associated colonic or other neoplasms are present in as many as one third of cases.[26]

It is especially important to consider fecal impaction as a possible cause of "diarrhea" in the elderly. Frequent, loose, watery motions can be expelled past a hard obstructing fecal mass, and if rectal examination is not performed, dangerous constipating drugs may be prescribed and result in complete obstipation. If questioned carefully, the patient may recall a long period of constipation preceding the "diarrhea." On the other hand, diarrhea resulting from unrecognized laxative abuse is not a common problem in patients past age 70. However, close questioning about any type of medication the patient may be using can avoid a needless work-up.

Systemic disease is less frequently a cause of diarrhea in the elderly than in younger patients. Nevertheless malabsorption syndromes of various etiologies, including celiac sprue, do occur and should not be dismissed offhand. The number of motions may not be excessive, but the patient may note an unusually bulky stool. Diabetes and hyperthyroidism can be associated with increased frequency of bowel motions as a prominent complaint, although there is generally no problem in establishing the diagnosis because of other obvious findings at the time.

GASTROINTESTINAL BLEEDING

Chronic occult blood loss in the elderly is frequently overlooked for long periods because symptoms resulting from the anemia are generally referred to other organ systems. Thus angina, congestive heart failure, or cerebrovascular insufficiency may appear as the major problem in a patient with significant anemia. While some malabsorption of iron can occur in elderly patients, iron deficiency is almost always a result of blood loss. Although a silent neoplasm, particularly carcinoma of the cecum, is the immediate concern, often a less serious lesion such as colonic polyps or peptic ulcer will be found.

Upper Gastrointestinal Bleeding

The major causes of upper gastrointestinal bleeding prove to be benign. Frank hematemesis is an uncommon presentation of gastric carcinoma. The causes of acute upper gastrointestinal bleeding in 100 consecutive patients over 70 admitted to the Coney Island Hospital and confirmed by endoscopy are seen in Table 1. It is obvious that peptic ulcer is by far the most common cause of upper gastrointestinal bleeding in the elderly. The majority of cases of bleeding occur in the absence of previous symptoms. For example, some patients with no previous symptoms may suffer massive bleeding from giant peptic ulcers, and gastric polyps can result in unexpectedly severe bleeding in an asymptomatic patient. Nevertheless, helpful clues should be sought in the history. Habitual ingestion of aspirin may lead to hemorrhagic gastritis or gastric ulcer. Occasionally hemorrhagic gastritis may develop after only a few aspirin tablets, but frank hematemesis or melena in such a patient more often indicates the presence of a pre-existing lesion such as duodenal or gastric ulcer. The discovery of a Mallory-Weiss cardioesophageal tear in the elderly suggests unusually intense vomiting and a thorough search should be undertaken for a potential underlying

Table 1. *Endoscopic Diagnosis in 100 Consecutive Patients over 70 with Upper Gastrointestinal Bleeding**

ETIOLOGY	AGE 70 TO 79	AGE 80 AND OVER	TOTAL
Gastric ulcer	15	16	31
Hemorrhagic gastritis	13	10	23
Duodenal ulcer	7	13	20
Cancer of stomach	3	4	7
Sarcoma of stomach	2	3	5
Esophageal varices	2	2	4
Gastric polyps	3	–	3
Gastritis in hernial pouch	1	1	2
Mallory-Weiss tear	1	1	2
Esophagitis	–	1	1
Cancer of esophagus	1	–	1
Hemorrhagic duodenitis	–	1	1
	48	52	100

*Excludes marginal ulcer

cause, such as biliary tract disease. Preoccupation with the bleeding itself can lead to overlooking a more important problem.

A history of blood transfusions, often preceding the bleed by decades, or the discovery of asymptomatic hepatomegaly or splenomegaly may be the only clue to the presence of bleeding esophageal varices which often are the initial manifestation of unsuspected chronic liver disease in the upper age groups.

Upper gastrointestinal bleeding may be the first manifestation of a bleeding diathesis such as diffuse intravascular coagulation secondary to gram-negative sepsis. The underlying event may be completely ignored if the accompanying shock is wrongly attributed to the blood loss. Evidence of purpura or bleeding elsewhere should alert the physician to the presence of a coagulopathy.

Traditionally, hematemesis associated with a symptomatic hiatus hernia has been attributed to esophagitis. However, we and others have found bleeding from the herniated gastric pouch to be as common as that from esophagitis.[22] Often the bleeding episode is severe. Paraesophageal hernia is particularly prone to bleeding from the gastric pouch. Esophagitis is found in less than 20 per cent of the cases of paraesophageal hernia. In a third of cases, a gastric ulcer develops in the herniated pouch and may be a source of gastrointestinal bleeding.[18]

Rectal Bleeding

The appearance of blood in the stool is always an alarming symptom. The casual attitude of so many elderly patients toward this finding is understandable, however, given their undue preoccupation with hemorrhoids as a source of so many of their ills. Unfortunately, in too many cases the physician will be content to accept this explanation for the bleeding especially when the hemorrhoids are conspicuous. In fact, hemorrhoids are not a common cause of rectal bleeding which appears for the first time in the elderly. *No episode of rectal bleeding should be ignored, no matter how minor!*

Rectosigmoid cancer is without question the most serious cause of rectal bleeding. In the majority of cases, this is no more than minor streaking although moderate hemorrhage can occur on occasion. Bleeding may be periodic and often precedes other overt symptoms of cancer by some time.

Bleeding is the most common clinical manifestation of a colonic polyp. There is a widely held option that barium enema and colonoscopy should be performed whenever a distal polyp is found, to exclude additional polyps or even malignancy in a more proximal location. While this is still impractical in every instance, extensive evaluation certainly appears advisable where a family history of colonic cancer exists or when polyps are pedunculated, larger than 0.5 cm or multiple.

Despite decades of often heated controversy over its premalignant potential, in several circumstances the colonic polyp can be justifiably regarded as the clinician's "sentinel" for cancer of the colon. The likelihood of finding malignancy within a polyp is directly related to size, degree of villous histologic change, and presence of a pedicle. Furthermore, the clearly benign polyp alerts the clinician to the possibility of present or future colonic cancer at other sites. Cancer of the colon is the most common malignancy in old age today with a prevalence rate of about 3 per cent after age 70. Curative resections are being performed in a growing number of patients, who then constitute a new risk group for future colonic cancer. Moreover, another "synchronous" or simultaneous cancer of the colon is present in about 3.5 per cent of patients with a newly discovered cancer of the colon, and a large number of these cancers escape detection[10,16] It is in these two circumstances—the newly discovered cancer, and the "cured" patient—that the role of the colonic polyp as "sentinel" can best be appreciated. Although only 10 to 20 per cent of a randomly discovered single cancer of the colon will be accompanied by a benign polyp, 60 per cent of patients who develop a second or "metachronous" cancer had a coexistent polyp at the time of the first operation.[17] Two and a half per cent of patients with a resectable curable cancer of the colon coexisting with an adenomatous polyp will develop a subsequent cancer, and the risk may rise to over 10 per cent when multiple polyps are found! In the case of simultaneous colonic cancers, three quarters of the cases are associated with a benign polyp.[16] In light of these data, one must view the colonic polyp not only as a source of a specific symptom in a patient, but also as a useful guide in selecting patients for more extensive evaluation.

When rectal bleeding occurs suddenly in association with abdominal pain and diarrhea in an elderly patient, the most likely cause is ischemic colitis. However, there are many atypical ways in which ischemic colitis may present. Pain may be transient, and the patient may even fail to recall it. While diarrhea is most common, bowel habits may remain unchanged, and even constipation may develop. Thus rectal bleeding may be the only symptom that the patient takes notice of.

The most common cause of massive rectal bleeding is colonic diverticulosis. Recent angiographic studies have shown that a right-sided diverticulum is responsible for bleeding in the overwhelming number of cases.[9] Characteristically, the onset is abrupt and occurs without premonitory signs or symptoms. Immediate angiography during the active bleeding has proved to be the most reliable means of diagnosis.

A previously unrecognized, but increasingly important cause of severe bleeding is the angiodysplastic lesion composed of submucosal vascular ectatic lakes. This lesion has a predilection for the proximal colon and is entirely asymptomatic. A relationship to aortic stenosis has been suggested but not proven. Angiography remains the only successful diagnostic tool.

ABDOMINAL PAIN

Chronic Abdominal Pain

The evaluation of persistent or recurrent abdominal pain in the elderly patient presents a greater challenge to the physician than in younger patients. The number of diagnostic possibilities increases with age; precise information regarding the character of the pain is often difficult to elicit; and the patient may be unable to distinguish a new symptom from other coexisting medical complaints. Nevertheless it is often possible to establish certain important features: nature and radiation of the pain, relationships to meals or bowel movements, and associated signs such as weight loss or fever. Currently available diagnostic methods can usually establish the presence of the most important causes, particularly neoplastic, biliary tract, peptic ulcer, or diverticular disease.

Cancer of the pancreas remains the most distressingly elusive of major gastrointestinal neoplasms. While the majority of patients will experience abdominal pain, this is often vague and poorly localized until invasion of continuous structures occurs. Certain rare manifestations may suggest the diagnosis and provide the impetus to undertake more extensive invasive diagnostic procedures. Thrombophlebitis, in the absence of trauma or chronic venous disease, may be an early warning sign. This is particularly significant in cases of recurrent phlebitis or phlebitis in an unusual location.

The sudden appearance of diabetes may precede overt symptoms of the tumor. An episode of acute pancreatitis without any underlying etiology can also be the first evidence of an early pancreatic lesion.

Mental changes, particularly depression, have long been suggested as an early sign of pancreatic carcinoma. When mental changes develop in an elderly patient, a diagnosis of reactive depression is often made and the accompanying weight loss is attributed to his mental status. Close questioning, however, may uncover ill-defined abdominal or back distress underlying his depressive state.

Pancreatic carcinoma is also the most common cause of nonbacterial thrombotic endocarditis, which is unlikely to be recognized unless embolization occurs.[6] Systemic emboli are the first manifestation of this endocarditis in 25 per cent of cases.

Acute Abdominal Pain

The majority of patients with acute onset of severe abdominal pain do not require urgent surgery. Nevertheless, surgery is necessary in one out of three patients over the age of 65, twice as often as in patients below this age. Multiple factors in this age group generally interact to frustrate the physician in these crucial situations. The history is often poor and confusing; the expected abdominal signs may be minimal or even absent; and decompensation of other organ systems such as the heart and lungs may result in symptoms that overshadow the abdominal complaints. When obtundation, confusion, or shock appears suddenly, an intra-abdominal catastrophe must be considered since in this circumstance, abdominal signs can be easily overlooked. Above all, the physician must remain on guard for the possibility of a medical cause of the acute abdomen. In the elderly, acute myocardial infarction, cardiac decompensation, pleuropulmonary problems, and diseases of the urinary tract are among the most common conditions simulating an acute abdomen.

Excluding cholecystitis, the most common cause of acute abdominal pain in an elderly patient, is, by far, intestinal obstruction,[5,29] and about 50 per cent of all cases are the result of an incarcerated hernia.[15] Often the signs of obstruction are atypical, with persistent rather than colicky pain, and occasionally pain may even diminish as gangrene develops. Bowel sounds are initially hyperactive but may be normal or even decreased by the time the patient is examined. Thorough search for an external hernia is important. Femoral hernias, which occur primarily in women, are particularly apt to be missed on cursory examination. Adhesions from previous surgery constitute the second most common cause of obstruction. No prior surgery, no matter how remote or small the incision, should be discounted. I have seen obstruction in an elderly patient with adhesive bands resulting from appendiceal surgery performed 60 years previously!

Obstruction of the large bowel can be more subtle than that of the small bowel. In an elderly patient, the former will most often be a result of a malignant obstruction. Signs of vomiting and severe distress may be conspicuously absent. The gradual or sudden onset of distention and obstipation may be the only complaints of a patient who otherwise appears well. By the same token, patients who appear late in the disease can appear critically ill. As many as one third of all elderly patients with rectosigmoid cancer have intestinal obstruction at the time of first presentation.

Volvulus of the colon is second only to malignancy as a cause of large bowel obstruction in the elderly.[15] In this age group, sigmoid volvulus occurs far more commonly than cecal volvulus. The latter is seen more often in women and is characterized by the acute onset of abdominal pain, nausea, vomiting, and distention.[24] By contrast, sigmoid volvulus predominates in men and symptoms evolve more slowly. Pain is present in the majority of cases, but abdominal distention and obstipation are the dominant symptoms. The presence of diarrhea does not exclude the diagnosis, however, and may be present in up to a quarter of cases. Close questioning will generally reveal a history of longstanding constipation. A background of mental illness and diminishing physical activity is quite common in this group of patients. Sigmoidoscopy may be both diagnostic and therapeutic if the explosive discharge of gaseous feces occurs during the procedure. Such decompression occurs in about half the cases. The usual signs of peritonitis are of limited value in determining if gangrene has developed and the patient must be closely observed for any change in his clinical condition.

While gallstone ileus accounts for less than 2 per cent of all cases of intestinal obstruction in patients over 65 years of age, it is among the most common causes of hernia-unrelated small bowel obstruction in this age group.[15] In the select group of women over age 70, obstruction by gallstones constitutes 20 per cent of all cases of obstruction when hernias are excluded. The vast majority of stones entering the gastrointestinal tract by biliary-enteric fistulas pass spontaneously with only a few impacting at the terminal ileum or sigmoid colon. The time-honored triad of radiologic evidence of air in the biliary tree, ectopic gallstone, and small bowel obstruction is found in fewer than 1 in 10 cases, although careful reading should show air in the biliary tree in about half the cases.[2] About 3 out of 4 of the patients are women, one fourth of whom have a history of definite biliary tract disease.

Acute appendicitis is so seldom considered in elderly patients that the impression is created that age confers immunity against this catastrophe. Quite the opposite is true. Acute appendicitis ranks immediately below obstruction in most series as a cause of major abdominal symptoms in the elderly.[5] Mortality is inordinately high probably because symptoms are often insidious, and inflammation rapidly progresses to perforation and localized or diffuse peritonitis.[32] Pain is initially mild without localization. Nausea and vomiting are common, and the patient is apt to have taken a purgative because of obstipation, which is a prominent symptom in about one fourth of the cases. Lassitude, drowsiness, and confusion often obscure the clinical picture. Vascular changes result in rapid necrosis so that in more than half the cases, the appendix is found to be gangrenous or perforated at surgery.

The incidence of acute pancreatitis rises with age, making this the most important nonsurgical, intra-abdominal cause of acute abdomen in the elderly. Although the expected laboratory abnormalities are generally found, the physician frequently feels uncomfortable with the diagnosis, particularly when the episode is accompanied by cardiorespiratory signs and minimal or atypically radiating pain, such as to the chest and/or lower abdomen. When atypical pain is combined with mental changes, signs of congestive heart failure, and concomitant EKG changes, the diagnosis can be confused with an acute myocardial event. In most cases pancreatitis is related to coexistent biliary tract disease, but in this age group it is important to consider unusual causes, particularly carcinoma of the pancreas, hyperparathyroidism, and hyperlipidemia.

Despite the fact that aging is generally viewed as synonymous with vascular disease, acute mesenteric infarction is frequently missed as a cause of acute abdominal pain in the elderly. Difficulty arises because there are no distinctive clinical features, and the disease mimics many other abdominal conditions. When loose, blood-stained motions and abdominal pain usher in the disease, the diagnosis is seldom overlooked. Often, however, diarrhea is absent or of short duration and gross blood is not seen. Sudden onset of abdominal pain, nausea, and vomiting dominate the initial clinical presentation and suggest upper gastrointestinal pathology. The initial response of the bowel to ischemia is hyperperistalsis with transient increase in bowel sounds accompanied by persistent and colicky pain. Bowel obstruction is often the major consideration at this point, and the frequent presence of "pseudo obstructive" pattern on x-ray examination only adds to the confusion. On rare occasions flat plate may show the characteristic "airless abdomen" which can aid in excluding obstruction. Throughout the course, abdominal findings are disarmingly mild or even absent, until peritonitis supervenes. Ileus and distention ultimately develop, and the pain, while usually reflecting peritoneal inflammation, may curiously decrease as gangrene ensues. At this point, restlessness, clouded sensorium, vascular instability, and cardiac decompensation supervene, producing a clinical picture which can be easily mistaken for a primary cardiac problem. When the diagnosis of mesenteric infarction is suspected, the slightest evidence, such as granulocytosis with marked shift to the left or hemoconcentration, may be grounds for mesenteric angiography and surgical intervention since prompt action remains the only hope for increasing survival in cases of major vessel occlusive disease. Diagnostic paracentesis may be useful when blood-stained fluid is noted, although this finding occurs late and indicates irreversible gangrene. The presence of an elevated serum amylase level is frequently cited as a cause for delay, but in actuality, elevations greater than 300 Somogyi units are distinctly rare.[27] In the uncommon situation of marked elevation of amylase whether in serum or peritoneal fluid, the decision to undertake surgery must rely upon other associated findings suggestive of vascular disease.

JAUNDICE

There is little evidence of clinically significant alteration of hepatic function with aging, despite the frequent demonstration of changes in size, histology, blood flow, and BSP excretion.[20] While transient hyperbilirubinemia and elevation in hepatic enzymes are often seen in association with major infectious illnesses, shock, and congestive heart failure, prolonged or progressive clinical jaundice indicates a specific hepatic problem.

Most series agree that malignant obstruction of the biliary system is the single most common cause of persistent jaundice in the elderly[11] and must therefore be foremost in the mind of any physician facing this problem. In over half the cases, a pancreatic neoplasm is responsible. Aside from varying degrees of pain, history may be discouragingly unrewarding. Progressive and intractable pruritus, although not specific for extrahepatic obstruction, may accompany or antedate the jaundice and indicates an obstructive element.

It is not surprising that choledocholithiasis is almost as frequent a cause of jaundice in this age group as neoplasms since gallstones can be found in up to one third of patients over 70. However, it is not generally appreciated that in a third of the cases, jaundice is unassociated with biliary colic.[11] The absence of significant pain adds to the confusion when mild cholangitis complicates the obstruction. In this circumstance, marked transaminase elevations may mistakenly lead to a diagnosis of hepatitis. The presence of fever or leukocytosis as well as a rapid fall in enzymes favors the diagnosis of cholangitis. On rare occasions, a palpable gallbladder may be present, either directly related to the ductal stone or secondary to a concomitant cystic duct calculus. The availability of newer diagnostic techniques such as endoscopic retrograde cholangiopancreatography (ERCP) or transhepatic cholangiography has greatly simplified the diagnosis in difficult cases, but these procedures cannot supplant careful clinical examination.

While jaundice caused by nonsurgical conditions accounts for a substantial number of cases in the elderly, it is much less common than in younger patients. Viral hepatitis is probably the most common medical condition but is infrequent in the absence of previous transfusions. Diagnosis may be delayed since symptoms are generally insidious without the profound anorexia and lassitude seen in younger patients. Weight loss, vague abdominal pains, and changes in mood or mentation are common. Mortality is particularly high after age 65, with a significant percentage succumbing to acute hepatic failure.[13]

Drug-related jaundice occurs almost as frequently as viral hepatitis in the elderly and can mimic extrahepatic obstruction as well as acute parenchymal injury. Since elderly patients frequently require several kinds of medication, often of varying degrees of hepatotoxicity, the offending drug may be difficult to pinpoint. Oral hypoglycemic agents, phenothiazines, and anabolic steroids are among the major causes of intrahepatic cholestasis. Hepatitis-like reactions, identical to viral hepatitis or even chronic active hepatitis, may be caused by drugs such as methyldopa (Aldomet) and INH. Patients are often unaware of the drugs that they are taking. The physician must pursue the patient's drug history thoroughly, particularly in cases in which combination drugs have been prescribed. Every preparation, however seemingly innocuous, must be identified. The relationship between the laxative oxyphenisatin and chronic active hepatitis was overlooked for decades simply because such preparations were not even considered as potential toxins. Discontinuation of the drug or drugs may be the only means of establishing the diagnosis.

Chronic liver disease and cirrhosis must be mentioned as a cause of jaundice in the elderly. In most instances, signs of portal hypertension will be found, particularly splenomegaly. In any patient with known longstanding inactive cirrhosis in whom signs of decompensation or sudden right upper quadrant pain develops, the possibility of hepatoma must come to mind.

SUMMARY

Gastrointestinal disease in the elderly often lacks many of the specific signs and symptoms found in younger patients. The clinician must be aware of this limitation and be prepared to follow slender leads in order to diagnose serious and life-threatening disease.

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Gastroenterology Division
Coney Island Hospital
2601 Ocean Parkway
Brooklyn, New York 11235

The Changing Face of Peptic Ulcer in the Elderly

Mohan Narayanan, M.D.,[*] *and*
Francis U. Steinheber, M.D.[†]

Peptic ulcer has not been widely regarded as a serious clinical problem in patients over the age of 65 since the majority of recognized cases appear between the third and fifth decade of life. Nevertheless autopsy and clinical surveys have amply demonstrated a prevalence rate in the elderly equal to and greater than that of younger age groups. More importantly, the elderly account for a disproportionate number of the serious complications and deaths from peptic ulcer.[25] One half of the patients found to have a peptic ulcer in McKeown's autopsy study of patients over 70 years of age died as a direct result of the disease.[15] While hardly representative, this serves to underscore the gravity of the disease when it appears in later life.[22] Despite this, many physicians still fail to appreciate the extent and serious nature of the problem.

A number of factors combine to reduce the awareness of geriatric ulcer disease. In an age group in which other diseases dominate the clinical picture, little attention is apt to be paid to disease considered minor by comparison. The clinical features are altered with age and often escape notice. The reduced size of the population at risk gives the erroneous impression of a reduced prevalence of the disease. Most important, a false impression that the elderly have outlived the disease is created by misinterpretation of widely quoted studies on the natural therapy of ulcer disease. A brief review of these studies will illustrate the misconceptions that underlie medical attitudes about this disease in the elderly.

NATURAL HISTORY

A consistent picture of the course of peptic ulcer has emerged from a number of studies on patients observed over a period of many years.[10,11,13,14] While most series are based on follow-up of hospitalized patients, several reflect the natural history as seen in an outpatient setting.[7,18,19] The conclusions of these studies are in general agreement: if observed long enough, more than half the patients with symptomatic ulcer disease will follow a serious course, and only one in four can expect to become asymptomatic. An even worse prognosis can be anticipated if bleeding is the initial reason for hospitalization. Approximately 1 in 5 patients can be expected to be hospitalized with this complication some time in the course of disease. It is obvious that the course of the disease is punctuated by events that would seem to make diagnosis inevitable. While a more optimistic note is sounded in the few outpatient studies available,[7,18,19] the picture is nonetheless notable for either entry into a permanent phase of clinical remission or eventual resort to surgery in 1 in 6 cases. In series based on follow-up of patients initially hospitalized for ulcer, surgery is twice as likely to be required (in approximately 20 to 40 per cent of patients with gastric ulcer, 40 to 50 per cent of patients with duodenal ulcer).[10,11] The patient whose disease appears before age 25 stands almost a 50 per cent chance of undergoing surgery at some time during its course.[21]

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[*] Gastroenterology Fellow, Gastroenterology Division, Coney Island Hospital, Brooklyn, New York

[**] Chief, Gastroenterology Division, Coney Island Hospital; Instructor in Clinical Medicine, New York University School of Medicine, New York, New York

Certainly in a disease in which a sizable proportion of cases never surface clinically, a distorted view of the virulence of the disease is created. However, the basic conclusions seem valid: the intensity of the disease fluctuates with the length of time the patient is observed. But after a period of 15–20 years, the disease is eliminated as a clinical problem through remission or manifestations requiring active surgical intervention. These studies lead to the following popular medical perception of the disease: peptic ulcer, which is viewed as a disease of early and middle life, will have run its course by the time the patient enters the later stages of life. According to this view, natural remission, overt serious complications, or remedial surgery will have eliminated the disease from serious consideration. It is thus easy to see how this common line of reasoning reduces the level of awareness necessary for clinical recognition of the disease in later life. It ignores an essential fact about peptic ulcer in later life, namely, that more than half the cases in patients over 60 appear for the first time.[12,22] Furthermore, closer inspection will show that a significant number of patients with established ulcers entering the sixth decade and beyond may be in a period of maximum susceptibility to major complications of the ulcer. For example, in Martin and Lewis's series, the disease had been present for a decade or longer in half the patients who developed hemorrhage.[14] Thus ignorance of the full extent of peptic ulcer problems in the elderly can be traced in part to incorrect interpretation of facts about the natural history of the disease. An additional factor is the change in clinical features with age.

CLINICAL FEATURES OF PEPTIC ULCER

Unlike the younger patient, the elderly patient is likely to present with a major complication as the first indication of the presence of the disease.[20] In many patients pain is not a prominent complaint. Fewer than half the patients will recall a history of previous symptoms.[12] When present, symptoms tend to be vague and often atypical. A pattern of pain with consistent relief after eating is frequently absent. Rather, pain may be nondescript, poorly localized, and often with misleading radiation. Weight loss and vomiting may be outstanding features, often leading the physician to confuse it with malignancy. Paradoxically, loss of appetite may be an additional symptom.

Secondary complications are particularly likely to divert attention from the existence of the ulcer. Occult blood loss, with anemia for example, frequently results in increasing angina, congestive heart failure, or mental changes. Penetration into surrounding structures may lead to deceptive symptoms in this age group. On the other hand, deeply penetrated, often large ulcers, may be entirely asymptomatic. Gastric ulcer, which is particularly notorious for its deceptive presentation, will be considered separately.

Acid Studies

There is general agreement that gastric acid secretion decreases with age. The diagnostic usefulness of acid secretory studies has been greatly diminished by safe and reliable endoscopic techniques. Even in young patients, acid studies are at best conclusively abnormal in only one third of patients with duodenal ulcer, although duodenal ulcer rarely, if ever, occurs below a maximal acid output (MAO) of 15 mEq per hour. Acid secretion decreases by 5 mEq per hour per decade in men, and by about half this value in women. There is little information available on secretory studies in ulcer patients over 70 years of age. It is clear, however, that levels are considerably below those established for younger patients and that duodenal ulcer can occur with a maximal acid output below 5 mEq per hour.

There is no level of acid below which gastric ulcer cannot occur and only complete achlorhydria rules out this possibility. The majority of cases of gastric cancer are associated with acid secretion, often of normal levels. In most instances secretory studies will not be helpful in differentiating a benign from a malignant ulcer.

The major indication at present for acid secretory tests appears to be in identifying those patients with possible Zollinger Ellison syndrome, or in evaluating symptomatic patients after ulcer surgery. Most studies agree that acid secretory tests have little value in helping to tailor a particular operation to various levels of acid secretion.

Although the Zollinger Ellison syndrome is found mostly in younger patients, 20 per cent of cases occur after 60 years of age and 2 per cent after 70. While few data on acid studies are available in this age range, there is no reason to believe that criteria developed in younger patients do not hold true in the older range, i.e., basal acid output/maximum acid output (BAO/MAO) or basal acid concentration/maximum acid concentration (BAC/MAC) of greater than 0.6. The availability of gastrin measurements has superseded acid studies in many cases.

COMPLICATIONS

Mortality in peptic ulcer disease is more closely related to age than to any other single factor.[8,23] Although patients over 60 constitute about 15 per cent of the ulcer population,[12] 80 per cent of ulcer deaths occur in this group.[25] In half the cases, a major complication is likely to herald the appearance of the disease.[12] About one fourth of patients over 60 years of age admitted to the hospital with peptic ulcer require surgery because of severe complications.[24] The frequent absence of a previous history often delays diagnosis and contributes to the increased morbidity. On the whole, when ulcer disease begins in the elderly, it is more likely to run a virulent course.[3] The presence of coexistent illness coupled with a hesitancy to consider surgery adds to the difficulty of dealing effectively with complications when they occur. The overall incidence of complications in a consecutive series of patients with peptic ulcer 70 years of age or older admitted to Coney Island Hospital is seen in Table 1.

Bleeding

Bleeding is the most common complication of peptic ulcer in the elderly[5,24] (Table 1) and accounts for one half to two thirds of all fatal cases.[22,25] Often the episode develops without warning. In fact, half the cases of bleeding peptic ulcer occur in the absence of previous symptoms.[29] The increasing tendency for hemorrhagic complications to develop with advancing age is well illustrated by the fact that one half of all cases of bleeding ulcer occur after the age of 50.[29] According to Pulvertaft, a patient over the age of 50 with peptic ulcer is twice as likely to suffer an episode of bleeding as the patient under 50.[18] In both instances, the risk of rebleeding is doubled if bleeding is the first symptom. Moreover this risk increases progressively with age to 7 per cent yearly after age 70.[19]

In patients over the age of 65 submitted to surgery for uncontrolled bleeding, a mortality rate of more than 20 per cent can be expected. While age-related reduction in cardiac, respiratory, and renal reserve contribute in large part to this high mortality, delay in surgery may further jeopardize an already marginally compensated patient. Several prognostic factors may be useful in determining when to operate. Obvi-

Table 1. *Complications in 100 Consecutive Patients over Age 70 Admitted with Peptic Ulcer*

COMPLICATION	GASTRIC ULCER	DUODENAL ULCER	COMBINED GASTRIC ULCER AND DUODENAL ULCER	TOTAL
Bleeding	40	41	2	83
Perforation	5	3	–	8
Severe abdominal pain	1	5	1	7
Obstruction	–	2	–	2
	46	51	3	100

ously the general medical status of the patient greatly influences the decision to operate, but it is well to remember that elderly patients may tolerate surgery better than a prolonged or recurrent hemorrhage.

The severity of the hemorrhage and, more importantly, the potential for rebleeding after admission must be accurately assessed to formulate a reasonable approach to management. Since the fatality rate rises several fold with recurrent hemorrhage, particular attention should be paid to factors which predispose to rebleeding. Massive bleeding, hematemesis, and hypotension are all associated with a higher frequency of recurrent bleeding.[17] Gastric ulcer has a disturbing tendency to rebleed in as many as one out of three cases.[17] In the elderly, where gastric ulcer is more likely to be a major possibility, it is essential that aggressive diagnostic measures be pursued. We have found endoscopy to be well tolerated in the elderly patient, and this should be performed as soon as the patient is stabilized. While we agree with the literature on the need for close observation when dealing with bleeding gastric ulcer, we would add, based on our own experience, that no less vigilance should be exercised in the case of duodenal ulcer.

In more than 75 per cent of cases, bleeding responds to conservative measures and immediate surgery can be avoided (Coney Island Hospital series). On the other hand, emergency surgery is required in a higher percentage of elderly patients. In Brook's series, 40 per cent of all cases of massively bleeding peptic ulcers occurred in patients over the age of 65. More ominously, in 80 per cent of fatal cases, massive bleeding was the first sign of the disease.[3]

While no arbitrary rules can be applied, no patient with major risk factors should be excluded from consideration for surgery because of age. In general, patients requiring particularly close observation include those with gastric ulcers, overt hematemesis,[4,17] and substantial blood loss as evidenced by shock,[4] hemoglobin less than 9 gm, or initial blood replacement requirement of over 1500 cc.[3] A previous history of hemorrhage, continued bleeding or rebleeding after admission,[23] and persistent, associated pain are additional factors which should prompt early surgical intervention. It is not clear whether prior salicylate ingestion imposes additional risks, but it appears to be less significant. In the final analysis, it is the critical observation of the patient's response to the bleed and his ability to tolerate blood loss that must guide the physician in managing him and in arriving at the crucial decision for surgery.

Antrectomy with vagotomy remains the surgical procedure of choice.[9] When the patient's condition does not permit the more extensive procedure, ulcer ligation and vagotomy with a drainage procedure is an acceptable alternative although a higher recurrence rate can be anticipated.

Perforation

Perforation ranks second only to hemorrhage in frequency and accounts for about a quarter of all ulcer-related deaths.[25] Not only does perforation occur two to three times more commonly in the elderly (approximately 10 to 20 per cent of cases), but mortality rates rise steeply with age. The risk of perforation doubles over age 50.[18] The rapidly destabilizing effect of a serious insult in a patient unable to tolerate major stress because of age-related infirmity is undoubtedly responsible for the high mortality.

Equally important is the frequent inordinate delay in operating in a situation where hours are critical. In fact, only half of all cases are brought to surgery within the first twelve hours because of a delay in recognizing the gravity of the patient's condition. The dismaying lack of overt symptomatology and absence of a prior history are the main reasons for failure to arrive at an immediate diagnosis. Symptoms are often poorly localized, and signs of peritonitis may be minimal. The usual expected signs of rigidity are frequently lacking and, while tenderness is usually present, it may be unimpressive in relation to the patient's distress. The decompensating effects on other organ systems may mask the primary abdominal events and direct attention elsewhere, particularly when congestive failure, shock, or obtundation is the immediate presenting problem. Deceptive localization of pain only adds to the confusion. For example, pain may be restricted to the right lower quadrant because of drainage of intestinal contents along the right paracolic gutter and may lead the clinician to a diagnosis of appendiceal abscess or a gynecologic problem.

It is unwise to rely solely on the presence of free air on x-ray to establish the diagnosis since this finding may be absent in one quarter of cases. Serum amylase is elevated above normal levels in about 20 per cent of cases but rarely exceeds 1000 Somogyi units. Paracentesis often reveals fluid with a very high amylase content, but the presence of bile in the fluid should mitigate against the diagnosis of acute pancreatitis. The probability of finding an elevated serum amylase increases directly with the length of delay in admission, and such increases are seldom seen in the first 6 hours. It is unclear whether the amylase to creatinine clearance ratio remains normal during acute perforation, but since the ratio does not increase during penetration of ulcer into the pancreas, it can be assumed that this also holds true for free perforations. A high degree of suspicion, coupled with a readiness to intervene surgically in a critically ill patient with indefinite abdominal complaints, remains the major means for reducing mortality.

Limitations of space do not permit us to comment extensively on the medical treatment of perforation, but the higher mortality rate and the fact that gastric ulcers account for a large number of perforations (Table 1) should temper enthusiasm for this approach in the elderly. In addition, the less frequent tendency of minor perforations to seal, together with decreased ability of an elderly patient to handle a major insult, makes resort to nonsurgical measures hazardous, unless there is good evidence of immediate and sustained response. In life-threatening situations, simple plication of the ulcer is usually the most advisable surgical approach, although in a stable patient a more definitive procedure is recommended.[9] Despite some divergence in published series, it appears that in the majority of cases of acute perforation, simple plication does achieve good results. In those cases with a preceding history of symptoms of longer than three months a recurrence rate of over 60 per cent can be anticipated. Clearly the judgment of the surgeon at the time must determine the surgical procedure to be used.

Obstruction

Gastric outlet obstruction complicates ulcer disease in about 10 per cent of patients over 60 years of age[20,24] and in only 2 per cent of all patients over 70 (Table 1). Unlike the other complications of peptic ulcer, virtually all patients will have a history of longstanding symptomatic disease. The usual symptoms of alteration of pain pattern, postprandial distress, and vomiting are not unlike that of younger patients. In addition, weight loss may be an especially disturbing feature leading the physician to suspect the presence of malignancy. If pain and vomiting are less apparent than profound anorexia and inanition, this suspicion may be intensified. Moreover, the elderly are particularly susceptible to the metabolic consequences of prolonged vomiting. Alkalosis, hypokalemia, and dehydration often lead to such profound weakness and debilitation that their underlying cause is often overlooked. Surgical relief of the obstruction is the only definitive approach to therapy. Vagotomy with antrectomy or, in difficult cases, with gastroenterostomy is the procedure of choice.

Intractability

Pain unresponsive to usual medical measures is an uncommon problem in peptic ulcer in the elderly and is a primary reason for surgery in less than 3 per cent of cases over the age of 70 (Coney Island Hospital series). The development of intractable pain usually indicates a superimposed complication such as obstruction or penetration into another organ. Duodenal ulcers penetrate most often posteriorly into the pancreas, or superiorly into the biliary tract or liver, while gastric ulcers tend to penetrate into the lesser sac or mesocolon. Radiation may be exclusively to the upper quadrants, back, flank or even chest, and usual measures afford no relief. When acute penetration into the pancreas is associated with hyperamylasemia, a diagnosis of pancreatitis and biliary tract disease is usually considered first. The amylase to creatinine clearance ratio remains normal, however. If the patient has no preceding ulcer symptoms, the appearance of constant, uncharacteristic pain may generate a fruitless search for various diagnoses suggested by the location of the pain radiation. For example, posterior penetration into the pancreas may result in localized chronic back pain. It is not unusual for this to mimic arthritic or disc disease of the spine, a particularly hazardous situation, since ulcerogenic drugs may be recommended for relief. The inevitable presence of a deformed bulb is usually of assistance in directing attention to the diagnosis.

A virulent variation of penetrated ulcer is the giant ulcer of the bulb (Fig. 1). This represents an extensive ulceration which replaces the major portion of the bulb. Since this lesion retains barium during an upper gastrointestinal series, it may, on cursory reading, resemble a normal bulb. A persistent collection of barium in what appears to be the

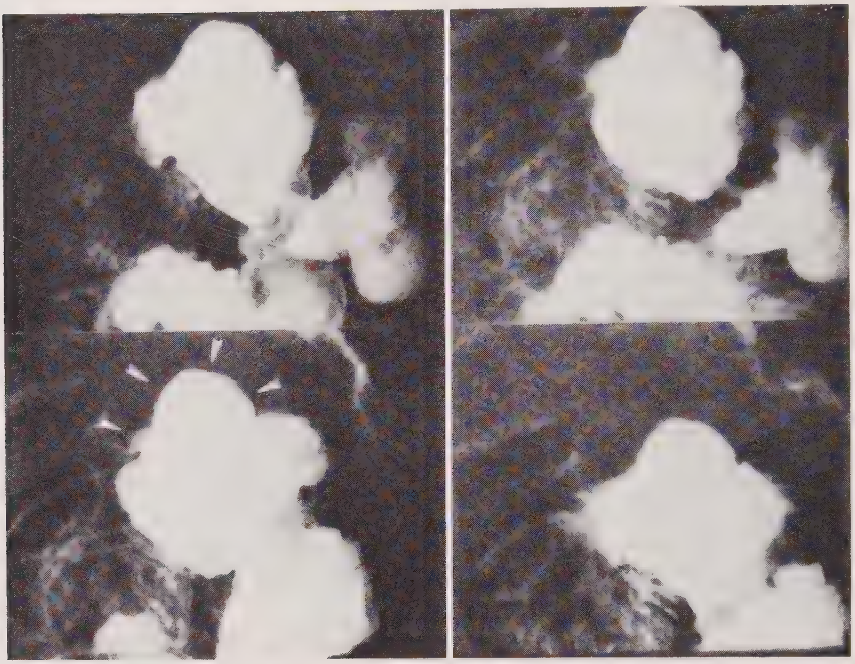

Figure 1. Giant ulcer of the bulb. Arrows outline huge crater. Patient was asymptomatic except for minor episode of upper gastrointestinal bleeding after hip fracture.

bulb should alert one to this diagnosis. In this circumstance, delay is hazardous, and surgery should be performed as soon as possible.

While the standard operation of antrectomy and vagotomy must still be recommended for uncomplicated cases with persistent symptoms,[9] in the future there will certainly be a place for newer techniques such as parietal cell vagotomy when scarring and obstruction are absent.

GASTRIC ULCER

Gastric ulcer is universally considered a disease of later life, reaching its peak incidence a decade later than duodenal ulcer. Although in most series duodenal ulcers outnumber gastric ulcers in the elderly,[5,20] two of every three ulcer deaths are related to gastric ulcer.[25] Male predominance is still found at a ratio of about 2 to 1,[6] with some suggestion that the ratio is further increased by a prepyloric location or associated duodenal ulcer. Because of its unpredictable behavior and disproportionate contribution to morbidity and mortality of ulcer in the elderly, special attention should be focused on gastric ulcer.

The clinical symptomatology of gastric ulcer is often subdued or bizarre in the elderly. Pain may be nonexistent or, conversely, very intense, often with unexpected radiation, for example, to the left upper or lower quadrant. Relationship to meals is inconstant, frequently worsening on ingestion of food. On occasion, weight loss of a severe degree may be the only presenting complaint. A poorly characterized state of ill health, not accompanied by definite abdominal complaints, may initially puzzle the physician. The commonly occurring juxta-cardia ulcers cause misleading symptoms by virtue of their location. Dysphagia, pain on swallowing, or regurgitation may mimic an esophageal neoplasm. It is not uncommon for the substernal pain to be mistaken for atypical angina or even a myocardial infarction. The patient with coexistent angina may be unable to differentiate the pain, thus adding to the dilemma. Chronic blood loss is more common in gastric ulcers than in duodenal ulcers, and the resultant anemia may lead to cardiac or cerebral symptoms, thus misdirecting the initial investigation.

The striking association of gastric ulcer with chronic ingestion of salicylates has recently received wide attention. It is especially important to elicit a history of salicylate consumption in the elderly who are notorious users of such medications for minor complaints, even as sedatives! The danger becomes particularly acute when the relief is sought from ulcer pain.

The high mortality from bleeding in gastric ulcer has been commented on previously,[6] especially as it relates to severity of initial bleeding and frequency of rebleeding. The explosive onset of complications without forewarning is an equally important factor, fully one half of gastric ulcer fatalities occurring in patients with symptoms of less than 4 weeks' duration.[8] As a rule, when dealing with serious bleeding from gastric ulcer, there should be little reluctance to resort to early surgery. On the other hand, prompt cessation of bleeding is an encouraging sign that surgery can be avoided. In our series, four out of five cases responded to medical measures. Surgery does not differ technically from that used for duodenal ulcer. However resections may be higher to include the ulcer, and vagotomy is not always necessary.

Despite the frequent resort to surgery, aggressive medical therapy frequently yields surprisingly good results. The well-recognized, long term recurrence rate of 50 to 75 per cent should not discourage a vigorous attempt at medical management under close observation of healing. In the elderly, healing rates vary widely and slow progression over several months to complete healing does not imply an increased recurrence rate. A counter argument has been made by Amberg[1] who found a 43 per cent mortality in a small number of patients over 70 with gastric ulcer who were treated medically. We feel strongly that cautious optimism is warranted if strict adherence is paid to an intensive antacid program and if progressive healing is observed, usually by endoscopy. Surgical intervention can be sought if the progress is deemed unsatisfactory.

Anatomic Features

While a lesser curvature location is found in gastric ulcers at all ages, there is a marked tendency for a more proximal location in elderly, 40 per cent being situated in a juxta-cardia or posterior wall position.[1] In general, about 85 per cent of gastric ulcers will be found within 9 cm of the pylorus.[27] The difficulty in radiologic detection in these locations accounts for a sizable number of cases being overlooked. An intrathoracic location of a gastric ulcer may occur in association with a hiatus hernia and is often missed. These pouch ulcers are particularly serious because of their propensity for bleeding or perforation into thoracic structures.[13]

Giant Gastric Ulcer

While this term is often used loosely, it should be limited to an ulcer larger than 3 cm.[26] This variety of ulcer tends to occur more frequently in the elderly. It is associated with particularly high complication rate, and is often difficult to differentiate from carcinoma[26] (Figs. 2, 3). Pain is highly variable, with the majority of patients exhibiting unexpected patterns of radiation (one quarter of the cases will radiate to the chest or retrosternal area and another quarter to the periumbilical or lower abdomen). Bleeding develops in 50 per cent of the cases, but perforation occurs much less commonly. An overall mortality rate of 20 per cent reflects the serious nature of a gastric ulcer that achieves this size. Medical therapy is far less satisfying than in smaller ulcers; only one in three can be expected to heal as opposed to better than three out of four smaller ulcers. Over half will recur, usually earlier than might be expected.

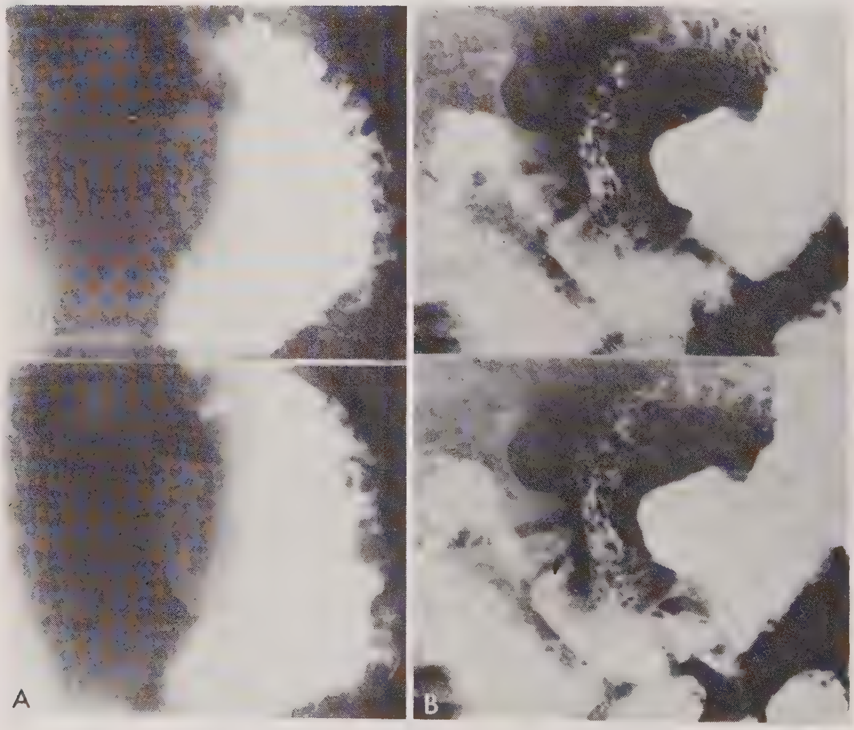

Figure 2. X-rays of giant gastric ulcers, benign versus malignant. *A*, Benign ulcer along lesser curvature. *B*, Malignant ulcer in antrum.

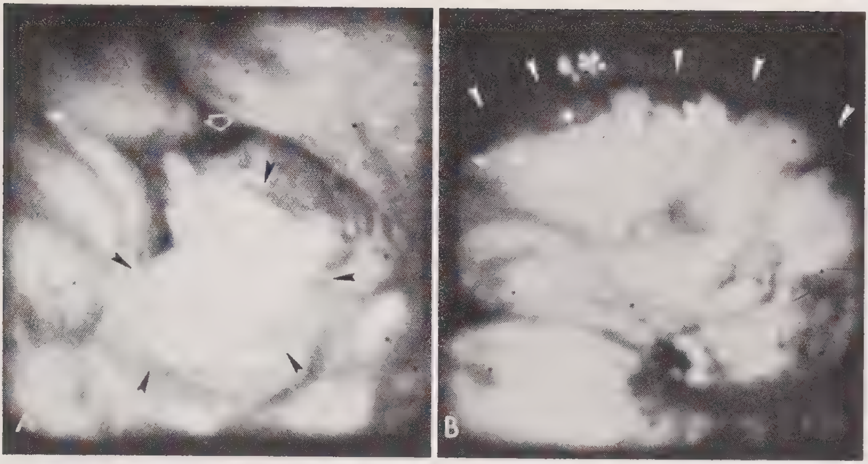

Figure 3. Endoscopic view of ulcers noted in Figure 2. *A*, Benign ulcer; small arrows outline well defined margin; large arrow indicates pylorus. *B*, Arrows outline raised nodular margins of huge ulceration. Both patients were asymptomatic except for upper G.I. bleeding.

Nevertheless, despite the overall pessimistic outlook, an intensive program of medical therapy is justified, provided that symptomatic relief is obtained quickly and continued progress of healing is closely monitored. We feel that in this particular circumstance repeated endoscopic follow-up is essential.

The Problem of Cancer

Despite a half century of controversy, debate continues on the relationship of gastric ulcer to gastric malignancy. There is little firm evidence to suggest that a gastric ulcer will become malignant in a clinically significant number of cases. While most long-term series will uncover a tumor in 1 to 3 per cent of patients with gastric ulcer[6,28] followed for more than 2 years, the majority are found within the first 18 months, suggesting that the initial diagnosis was incorrect. In other cases, malignancy develops away from the site of the ulcer.

In the elderly, especially those with large gastric ulcers, the overriding concern is to avoid mistaking an ulcerated malignancy for a benign ulcer (Fig. 2). It is especially disturbing that even after thorough assessment, unsuspected malignancy is later found in about 4 per cent of cases in most series.[16] The widespread use of endoscopy, biopsy, and cytology with close follow-up should reduce this risk to less than 1 per cent. Furthermore, superficial mucosal carcinoma is found in about 5 per cent of specimens after gastrectomy. Since symptoms have rarely been present for longer than 18 months in these cases, it is doubtful that this represents malignant degeneration of a previously benign ulcer.[16] Nevertheless the majority of simple ulcers, no matter how large, will prove to be benign. If healing rate fails to progress as expected, or if symptoms reappear, surgery should be considered.

MEDICAL TREATMENT

Antacids remain the foundation of medical therapy of peptic ulcer. There is no dispute over the effectiveness of antacids in relieving pain, but controversy continues to surround their usefulness in promoting healing. Nevertheless, we remain convinced that antacids are the most valuable form of medical therapy, despite the inability of controlled studies to demonstrate acceleration of healing. Proper use requires hourly administration of one ounce of a liquid preparation throughout the day.

Because of the demonstration of acid rebound with calcium carbonate preparations as well as the potential for hypercalcemia and renal impairment, we avoid the use of these compounds. Although the sodium-containing liquid antacids constitute a potential problem of salt overload in patients with congestive heart failure, we have not experienced any major difficulty with these preparations. Nevertheless salt overload must be considered when dealing with a patient in marginal cardiac compensation.

Prolonged ingestion of magnesium-aluminum hydroxide compounds may lead to a phosphate depletion syndrome, but this is seldom encountered clinically. This syndrome is characterized by anorexia, weakness, and bone pain. Marked decrease in the urinary and serum phosphate, and hypercalciuria are invariable findings in this syndrome. Diarrhea will frequently occur with the magnesium-containing compounds, and the alteration of these preparations with constipating aluminum compounds may be useful on occasion.

Despite their demonstrated effect in reducing protein-stimulated acid secretion, we generally discourage the use of anticholinergic agents in elderly patients. In clinical practice, they do not appear to provide additional benefit to antacids, and the urinary, salivary, ocular, and cardiac side effects are potentially serious complications in this age group.

Several newer therapeutic agents including depepsin and carbenoxolone, have not received wide acceptance in this country, despite evidence of their efficacy. Depepsin (amylopectin sulfate) is a synthetic sulfated polysaccharide with anti-peptic activity which appears to have beneficial effects in promoting healing.

Carbenoxolone, a synthetic derivative of glycyrrhetinic acid, has been shown to accelerate the healing of gastric ulcers. It appears to exert its effect locally by acting directly on mucosal cells and gastric mucus without affecting acid secretion. Its major side effects of sodium and water retention and hypokalemia limit its potential usefulness in elderly patients.

The most important advance in the medical treatment of peptic ulcer is the discovery of the H_2 histamine receptor antagonists. The action of histamine is mediated at two known receptor sites. The site of action which is blocked by classic antihistamines, such as on smooth muscle of gut or bronchioles, is called the H_1 receptor site. Receptor sites not affected by these antihistamines, such as on the gastric parietal cell, have been designated H_2 receptor sites. Compounds which block the action of histamine at the H_2 receptors are the most effective available inhibitors of physiologically stimulated acid secretion, achieving better than 90 per cent reduction at maximal doses. The latest modification of these compounds, cimetidine, is relatively nontoxic. While these are controlled drugs in this country at present, there is reason to believe that they may represent the most effective form of therapy for the future.

Certain prostaglandin derivatives have been shown to be effective by the oral route in decreasing acid secretion by up to 60 to 90 per cent, but these have not yet been applied clinically.

No discussion of treatment of peptic ulcer in the elderly would be complete without reference to the use of gastric irradiation.[2] In practice, this modality is limited to patients who constitute a prohibitively poor risk for surgery. A wide body of experience in specialized centers attests to the effectiveness of gastric irradiation in promoting the healing of gastric and duodenal ulcers in most cases. Complete achlorhydria or 50 per cent reduction in maximum acid secretion can be obtained in virtually all cases, and this reduction will continue for several years in half the cases. There do not appear to be any significant side effects although the long term development of radiation nephritis has been recently emphasized.

SUMMARY

The elderly patient presents a challenge to the physician both in recognition of peptic ulcer disease and in long term management. Only with close observation and an awareness of the higher complication rate can a successful therapeutic approach be developed.

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Gastroenterology Division
Coney Island Hospital
2601 Ocean Parkway
Brooklyn, New York 11235

Symposium on Geriatric Medicine

Arthritis in the Elderly

An Overview

Harry Bienenstock, M.D., and K. Ranjit Fernando, M.D.***

Arthritis and rheumatic diseases are, perhaps, the major cause of disability in the elderly. Newer techniques have increased our understanding of the underlying mechanisms of many of these disorders. There is, however, an even greater area in which our knowledge is limited and in which diagnosis and treatment remain empirical.

Knowledge of a normal state is a prerequisite to an understanding of disease. In this paper, a brief introduction of normal joint structure and function precedes the discussion of those rheumatic conditions that most frequently affect the elderly.

Structure and Function of Joints

Arthritis most frequently affects *diarthrodial* (synovial) joints which consist of rigid cartilage or cartilage-covered bones united by a fibrous capsule that is lined by synovial membrane. This cartilage is devoid of nerve endings. It receives its nutrition via an exchange of materials between the cartilagenous matrix and the synovial fluid. The adult chondrocyte does not divide, does not synthesize DNA, and does not exhibit mitotic activity. Nevertheless, it is metabolically active, rapidly incorporating sulfate and synthesizing RNA. The cartilage matrix is composed of collagen, protein polysaccharides, water, and minerals.

Synovial membrane is a vascular connective tissue that lines the inner surface of the capsule and abuts against but does not cover the articular cartilage. It consists of two types of cells: type A, which perform absorptive and digestive functions, and type B, which produces hyaluronic acid and protein complexes. The synovial fluid is composed mainly of an ultrafiltrate of plasma and hyaluronate elaborated by type B cells. Maintenance of joint function is the result of a complex set of mechanisms that include the lubricating properties of joint fluid, self lubrication at the site of weight bearing where fluid is "squeezed" out of cartilage, and the irregular surface of normal cartilage that entraps small amounts of fluid and distributes joint pressure over a large area.[3]

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*Chief, Rheumatology Division, Coney Island Hospital; Chief, Rheumatology Division, Long Island College Hospital; Assistant Attending Physician, The Hospital for Special Surgery; Assistant Clinical Professor of Medicine, Cornell University Medical College

**Fellow in Rheumatology, Long Island College Hospital and Coney Island Hospital

Normal joint function depends on the architectural integrity of bones, articular surfaces, capsules and restraining ligaments. Adequate joint movement and muscle contraction are necessary to maintain normal joint function.

Aging of Joints and Connective Tissue

Aging has been described as changes occurring with the passage of time that determine the lifespan that is characteristic for the species.[26] It is often difficult to discern the fine line that separates degenerative disease from changes that are an integral part of the aging process. As collagen ages, it exhibits reduced capacity for swelling, increased resistance to digestion by collagenase, and a higher calcium binding capacity. The elastic fibers lose their resiliency and they fray, fibrillate, and calcify. The content of the ground substance decreases.

Changes associated with aging may begin in both articular and non-articular cartilage as early as age 20.[26] The gross appearance turns from bluish translucent to yellowish opaque with loss of chondroitin sulfate and deposition of fat. The surfaces become frayed and begin to shred. Cracks appear and small pieces of cartilage are broken off, leading to deep vertical fissures. Once the deepest layer of cartilage is removed, subchondral bone is exposed and new bone formation may take place. No definitive criteria have been established to differentiate the appearance of the normal aging cartilage from that seen in degenerative joint disease. One is therefore faced with the dilemma of determining what changes are part of the "normal" aging process and what changes are due to degenerative disease.

DEGENERATIVE JOINT DISEASE

Cartilage degeneration, eburnation of bone, and bony prominences at joint margins, called osteophytes, are characteristic signs of degenerative joint disease (osteoarthritis). The disease is widely distributed in the population but predominates in the elderly. A British population survey[17] reported that 87 per cent of women and 83 per cent of men between 55 and 64 years had radiographic evidence of osteoarthritis. Of this group, one-fourth were symptomatic. Similar findings have been noted in other studies.[10] A variety of causes in addition to aging determine the rate at which cartilage undergoes degeneration. When predisposing factors initiate or accelerate the progress of degenerative joint disease, the term secondary osteoarthritis (Table 1) is used.

Primary Degenerative Joint Disease

Primary degenerative joint disease is a condition in which none of the factors listed in Table 1 can be demonstrated in a patient with osteoarthritis. This condition affects middle-aged and elderly people of both sexes to a similar degree. Symptoms are usually confined to a few joints, the most frequently involved sites being the distal interphalangeal joints of the hands, knees, hips, first carpometacarpal joint, first metatarsophalangeal joint, cervical spine, and lower lumbar spine.

Table 1. *Causes of Secondary Osteoarthritis*

Genetic	*Metabolic and hormonal factors*
Congenital dysplasia and dislocation of the hip	Obesity
Osteochondroses, e.g., Legg-Calve-Perthes disease	Diabetes
Slipped capital femoral epiphysis (adolescent coxa vera)	Acromegaly
Trauma to joint or adjacent bone	*Dietary*
	Kashin-Beck disease*
Pre-existing disease of the joints	*Iatrogenic*
Rheumatoid arthritis	Intra-articular corticosteroids
Septic arthritis	
Gout	
Pseudogout (chondrocalcinosis)	
Neurogenic arthropathy	
Aseptic necrosis	

*A condition, apparently related to intake of grain in endemic areas (Eastern Siberia and Manchuria), that results in articular changes indistinguishable from osteoarthritis.

Pain on motion, localized joint stiffness of short duration following periods of rest, and joint deformity without signs of inflammation are characteristic clinical findings in patients with osteoarthritis of the hands. Kellgren and Moore[18] consider the bony prominences at the margins of the distal interphalangeal joints (Heberden's nodes) of the hands to be an integral part of the clinical picture of primary generalized osteoarthritis. Others[27] feel that this feature need not be present in the generalized disease. Bony swellings at the proximal interphalangeal joints (Bouchard's nodes) are frequently confused with the soft tissue swelling of these joints seen in rheumatoid arthritis (Fig. 1).

In the lower extremities, functional shortening of a limb may result from flexion deformities at the hip. The patient may walk with a limp, and experience difficulty rising from a low chair and climbing stairs. Local joint tenderness, crepitus, and limitation of movement are early signs of knee disease. Later, erosion of cartilage in the medial or lateral compartment may lead to varus or valgus deformities. These changes are invariably accompanied by quadriceps muscle atrophy. Surprisingly, primary osteoarthritis involving the ankle, a major weight-bearing joint, is rare.

Degenerative disease of the spine is a common cause of local and referred pain. It may result from disease of the intervertebral discs, apophyseal joints, or vertebral bodies. Degenerative changes are most frequently seen at C5, T8, and L3–4, the sites of maximal spine motion. Nerve root compression by a prolapsed disc or bony foraminal osteophyte may produce radicular pain and/or paresthesias along the distribution of the affected nerve root. At times, cervical disc disease may produce myelopathy in the absence of radicular signs or an osteophyte in the cervical spine may compress the vertebral artery, producing vertigo and visual disturbances.

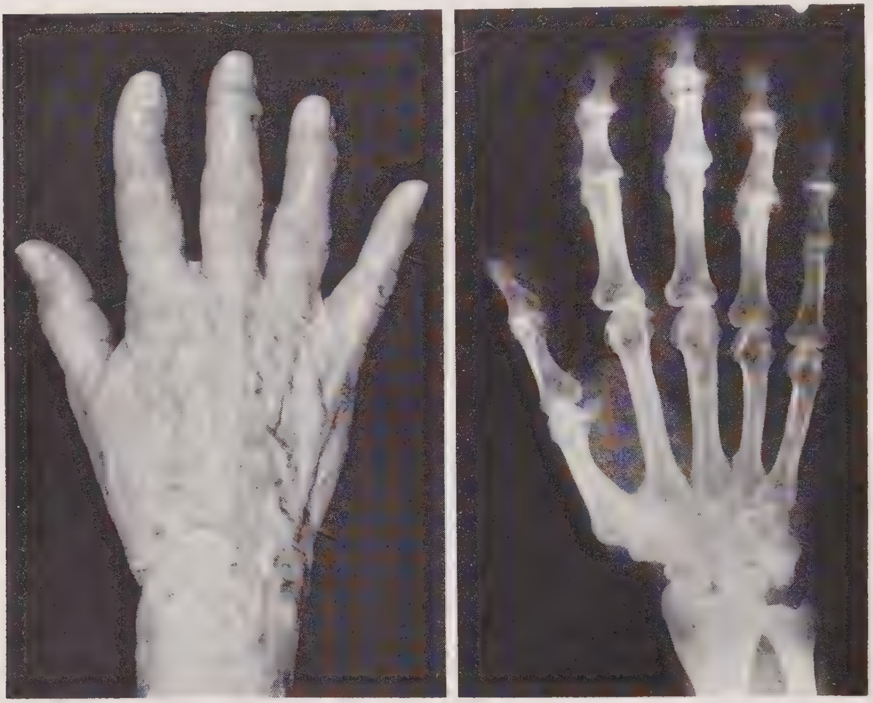

Figure 1. Hand of a patient with osteoarthritis superficially resembling rheumatoid arthritis. *Left,* Bony enlargement of distal (Heberden's) and proximal (Bouchard's) nodes. *Right,* X-ray showing irregular narrowing of distal and proximal interphalangeal joints with adjacent osteophyte formation. The metacarpophalangeal joints are normal in appearance.

Radiographic signs of osteoarthritis may bear little relationship to the clinical picture. Initially, the x-ray film may appear normal. Localized joint narrowing, marginal osteophytes, subchondral sclerosis, bone cysts, and erosions may all be observed with the passage of time.

An inflammatory type of degenerative joint disease called "erosive osteoarthritis"[8] is occasionally seen in women of menopausal age. The patient frequently experiences painful throbbing paresthesias of the hands, especially at night. The small joints of the hand are often swollen and red. Less commonly involved are the knees and cervical spine. Joint erosion, narrowing of the joint space, and marginal bony proliferation are seen on the radiograph. The sedimentation rate, elevated during the acute phase, usually returns to normal with quiescence of the inflammatory process.

Treatment

Relief of pain and associated muscle spasm and the maintenance of joint function are the prime objectives of treatment of degenerative joint disease. In many instances, relief may be obtained from aspirin in moderate doses (600 mg three or four times a day). Aspirin is analgesic, anti-inflammatory, and inexpensive. Patients with a history of intolerance or allergy to aspirin may be treated with acetaminophen or dextropropoxyphene for analgesia. If pain and/or inflammation persist, any one of a number of nonsteroidal agents may be tried. Indomethacin and phenylbutazone will frequently produce significant relief of pain and reduce the signs of inflammation. Newer nonsteroidal agents that have recently emerged in the United States or abroad include the proprionic acid derivatives, ibuprofen, fenoprofen, naproxen, and the indole derivative, tolmetin. They all appear to have a degree of effectiveness similar to aspirin. One should be thoroughly familiar with the potential side effects of all the aforementioned drugs before initiating therapy. The adage "primum non nocere" should always be kept in mind when treating this "benign" disease. The judicious use of local corticosteroid injection may produce symptomatic relief for days to months. Frequent joint injections should be avoided as local corticosteroids have been shown to damage articular cartilage.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is the most common form of inflammatory arthritis. Morning stiffness, joint pain, and swelling (frequently symmetric) are its cardinal features. Subcutaneous nodules may develop over bony prominences and about the extensor aspects of joints. The lack of clinical and laboratory parameters that will definitely establish the diagnosis has led to the establishment of a set of "criteria" for classification:[25] the large number of exclusions (20) appended to the criteria should serve to emphasize the importance of a careful work-up and the need for a period of observation before the diagnosis is established with reasonable certainty.

Although most commonly seen in women between 20 and 40 years of age, rheumatoid arthritis may occur in both sexes from infancy to old age. Ehrlich, Katz, and Cohen[9] have studied 79 patients over 60 years of age, 43 in whom the disease began after age 60. Gibson and Grahame described 12 patients with seropositive rheumatoid arthritis whose average age of onset was 79 years (range 70 to 88 years).[12] Others who have reported on rheumatoid arthritis in the elderly include Cecil and Kammerer[6] and Moseman.[23]

With increasing age, the female to male ratio declines.[6,9] The sedimentation rate is frequently markedly elevated and rheumatoid factor is present in the serum in a higher titer than in younger patients. Extra-articular manifestations, nodules, erosions, and arteritis may be less common.

Extra-articular manifestations of rheumatoid arthritis are usually seen in patients with high titers of rheumatoid factor in the serum. Rheumatoid vasculitis of small and medium sized vessels results in teliangiectasia, skin ulcerations, neuropathy, digital gangrene, and visceral complications such as mesenteric infarction. A variety of cardiac and pulmonary changes may occur.

Atlantoaxial subluxation, frequently a cause of occipital headache, may, at times, result in quadriparesis or sudden death.[21] In its early acute phase, cricoarytenoid arthritis causes pain on swallowing. Progressive reduction of cricoarytenoid joint motion may lead to fixation of the vocal cord in adduction and upper respiratory tract obstruction. Early recognition and prompt treatment may be life saving.[2]

Nerve compression resulting from proliferation of synovium in the wrist and ankle may lead to pain and paresthesia of characteristic distribution in carpal and tarsal tunnel syndromes.

Treatment

Drug therapy in rheumatoid arthritis should be directed toward the relief of pain and inflammation and arrest of the progress of the disease. These principles apply to young and old alike.

Aspirin remains the mainstay of treatment and should be used in doses sufficient to produce a significant anti-inflammatory as well as analgesic response. If aspirin in doses of 5 to 6 gm per day does not produce the desired analgesic effect, codeine, dextropropoxyphene, or pentazocaine may be added to the treatment program. Nonsteroidal anti-inflammatory agents may be employed as discussed under the heading Degenerative Joint Disease. It is important to bear in mind that inadequate relief of pain retards one's ability to carry out an effective program of physical therapy and rehabilitation.

If significant signs of inflammation persist for 6 to 8 weeks after institution of the above treatment program, consideration should be given to the use of gold salts. After initial "test" doses of 10 and 25 mg of gold salt—gold sodium thiomalate (myochrisine) or gold sodium thioglucose (Solgonal)—the patient is treated with weekly intramuscular injection of 50 mg of the salt until clinical signs subside or a total of 1 gm of the salt has been administered. If the desired result has been obtained (reduction of inflammation and other signs of remission), the patient is maintained on a monthly dose of 50 mg. In the absence of the desired response, the drug should be discontinued.

Gold should be administered with caution. Patients must be made aware of the possible dermatologic, hematologic, and renal complications of therapy. Complete blood counts, platelet estimations and urinalysis should be done frequently. It is best to inform the patient that it will take a number of months until the effects of treatment are discernible. If gold salt therapy proves ineffective or produces toxicity, alternative treatments with hydroxychloroquine, penicillamine, or immunosuppressive drugs may be considered. The scope of this paper does not permit discussion of these forms of treatment.

A word about corticosteroids is in order. They do not alter the course of rheumatoid arthritis. They reduce pain and increase the sense of well-being. Unfortunately, continued use may result in a wide variety of side effects as well as drug dependence. In individual cases, small doses of prednisone (2.5 to 7.5 mg) may be helpful in maintaining function in a patient with active rheumatoid arthritis. The goal should not be to completely obliterate pain and inflammation but to reduce them to tolerable levels.

OTHER FORMS OF INFLAMMATORY ARTHRITIS

Ankylosing Spondylitis, Psoriatic Arthropathy, Reiter's Syndrome, Enteropathic Arthropathy (the Spondylarthritides)

The active phase of these diseases tends to occur in younger patients with the possible exception of psoriatic arthropathy. In later life, however, patients may present with residual manifestations of any of these disorders. Spondylitis is present in a large proportion of patients with these diseases. From 80 to 90 per cent of patients with spondylitis have been shown to be positive for HLA–27, one of the histocompatibility antigens in man.[4] When peripheral joints are involved in ankylosing spondylitis, Reiter's syndrome, and the arthropathy accompanying ulcerative colitis or regional ileitis, the large joints are more frequently affected. In psoriasis, the distal interphalangeal joints of the hands and feet are often involved. In almost all instances, these patients are seronegative for rheumatoid factor, lack subcutaneous nodules, and experience a milder, more self limited course than those with rheumatoid arthritis.

SYSTEMIC LUPUS ERYTHEMATOSUS

In the elderly, the diagnosis of systemic lupus erythematosus can be easily missed.[11] Joint inflammation, insidious in onset, is milder and shorter lived and results in residual deformity less frequently than in rheumatoid arthritis. Serositis is less common in elderly patients than in younger patients. Older patients with the disease may develop fibrous and soft tissue changes about the small joints of the hand. Subluxations in the absence of joint erosions on radiographic examination may be seen. In many instances, symptoms abate with aspirin or low dosage corticosteroids. A lupus-like syndrome may be caused by a variety of drugs, including procainamide, hydralazine, and diphenylhydantoin, all frequently used in older patients. Clinical features of the "iatrogenic" disease are skin rash, lymphadenopathy, pleuritis, and pericarditis. Renal abnormalities are notably absent. Laboratory findings include the presence of antinuclear antibodies in blood, L.E. cells, anemia, leukopenia, and thrombocytopenia. Antibodies to double-stranded native DNA seen in systemic lupus erythematosus are absent in drug-induced disease. Discontinuation of the offending agent results in cessation of symptoms and normalization of laboratory parameters in most instances.

PROGRESSIVE SYSTEMIC SCLEROSIS

The incidence of scleroderma adjusted for age at diagnosis increases steadily, reaching a peak of 7.6 per million population for persons 65 years and older.[22] Polyarthralgia and joint stiffness of the fingers, wrists, knees, and ankles are early symptoms. Morning stiffness may simulate that seen in rheumatoid arthritis. In a small percentage of patients, significant warmth, redness, and swelling may be observed. Diffuse swelling of the extremities is followed by gradual loss of subcutaneous tissue and "skeletonization." Periarticular and soft tissue calcifications may be seen on x-ray as may resorption of the distal tufts. Cardiac, pulmonary, gastrointestinal, and renal complications may have a significant effect on the course of this disease.

GOUT

There is little to distinguish the clinical features of gout in the elderly from those seen in younger patients. The peak incidence of acute gouty arthritis is in the fifth decade in men and the sixth decade in women. Of 354 patients with gout reported by Grahame and Scott,[14] 12.7 per cent had their first attack after age 60. In women, the incidence rose from a premenopausal level of 7 per cent to 29 per cent after age 60. Elderly patients frequently develop hyperuricemia as a result of taking diuretics for cardiac or renal disease. Metabolic conditions associated with gout include obesity, atherosclerosis, and diabetes mellitus.

The diagnosis of gout is established by noting the presence of negatively birefringent crystals in synovial fluid. The serum uric acid level is usually elevated. Initially a therapeutic test with intravenous colchicine (2 mg intravenously as a single dose) should be tried. The patient may then be maintained on oral colchicine for a number of weeks to prevent recurrence of an acute attack. Other drugs that are effective in aborting an acute attack are phenylbutazone and indomethacin. Persistent hyperuricemia (serum uric acid levels greater than 10 mg per 100 ml), tophi, and chronic renal disease are reasons to consider the use of drugs that reduce the level of the serum uric acid. Allopurinol, a xanthine oxidase inhibitor, is very effective in lowering serum uric acid levels, and is the drug of choice in patients with reduced renal function. Probenecid and sulfinpyrazone are effective uricosuric agents that must be used with caution in the presence of renal disease.

PSEUDOGOUT

Unlike rheumatoid arthritis and gout, "pseudogout" has a clear predilection for the elderly. Thirty-three of 43 patients with chondrocalcinosis reported by Moscowitz[24] were over the age of 60. This age distribution is typical of most series. The syndrome is characterized by an acute or chronic arthritis, and weakly positive birefringent monoclinic or triclinic crystals of calcium pyrophosphate dihydrate (CPPD) in synovial fluid, and calcification of articular cartilage. CPPD may also be demonstrated by x-ray diffraction. The pattern of arthritis varies from an intermittent acute type that may mimic true gout to a chronic progressive arthritis affecting large joints, especially the knees and hips. Except for the presence of typical cartilage calcification, the radiographic picture is indistinguishable from degenerative joint disease. Acute symptoms are usually short lived and may be effectively treated with analgesic nonsteroidal anti-inflammatory agents or intra-articular injection of corticosteroids. Colchicine is effective in a small percentage of patients.

Deposition of CPPD in cartilage has been reported in many conditions including diabetes mellitus, hypoparathyroidism and hyperparathyroidism, hypothyroidism, Wilson's disease, acromegaly, gout, Charcot joint, and, on rare occasions, in rheumatoid arthritis and systemic lupus erythematosus.

INFECTIOUS ARTHRITIS

Infectious arthritis is the one form of arthritis in which "time is of the essence." An overlooked septic joint may result in rapid destruction of articular cartilage and even death as a result of septicemia.

Elderly patients are particularly susceptible to development of septic arthritis. Of 78 adult patients with septic arthritis reported from the Mayo Clinic, 40 were over the age of 60.[19] In another series 13 of 19 were over 60 years of age.[29] The most common organisms were staphylococcus, streptococcus, gonococcus, meningococcus, pneumococcus, and a variety of gram-negative organisms. Tubercle bacilli and fungi may also be isolated from the joints.

Predisposing factors in the elderly include (1) underlying chronic disease, e.g., diabetes mellitus, malignancy, alcoholism, uremia; (2) extra-articular infection such as pneumonia, bacterial endocarditis, urinary tract infection, osteomyelitis, or skin infection; (3) use of immunosuppressive drugs and corticosteroids. A point that deserves special emphasis is the higher incidence of septic arthritis in rheumatoid arthritis. Aspiration, gram stain, and culture of swollen joints should be the rule in patients with rheumatoid arthritis when there is the slightest suspicion of infection.

The key to diagnosis is careful attention to detail. Aseptic techniques should be employed to aspirate the joint. Gram stain and appropriate aerobic and anaerobic cultures should be taken. If the joint fluid appears purulent and/or the white cell count and polymorphonuclear cell count are high, appropriate parenteral antibiotic therapy should be instituted immediately after blood, urine, and throat cultures have been taken. Since it has been clearly demonstrated that bactericidal levels of antibiotics can be achieved in joint fluids, surgical drainage is now reserved for chronic joint infection or joint infection unresponsive to adequate parenteral antibiotic treatment.

POLYMYALGIA RHEUMATICA

Whereas the previously described forms of arthritis and connective tissue disorders occur to some degree in all age groups, polymyalgia rheumatica is a syndrome confined to the elderly. In fact, most criteria exclude patients under 50 years of age.[15] It usually manifests itself initially as symmetric shoulder or pelvic girdle stiffness and pain. Complaints of generalized fatigue, morning stiffness, anxiety, recent weight loss, and other "nonspecific" symptoms are common. True muscle weakness is absent as is muscle atrophy. On occasion, swelling of the soft tissues of the hands in the absence of joint redness or warmth may be present.

The vagueness of the symptoms in polymyalgia has resulted in the false labelling of many patients with this condition as having "functional" disease. This is especially true in overcrowded screening clinics of hospitals and busy practitioners' offices. The laboratory findings fall within the normal range with the exception of uniform elevation of the sedimentation rate—invariably above 50 mm per hour (Westergren). Significant anemia, muscle enzyme elevation, or presence of antinuclear antibodies should lead one to search for the presence of other conditions. Electromyography and muscle biopsy findings are normal or nonspecific. Most importantly, this syndrome must be differentiated from other connective tissue disorders, malignancy, infection, fibrositis, and other forms of non-articular rheumatism.

Once other conditions have been reasonably excluded, a trial of 20 to 30 mg of prednisone for 1 to 2 weeks should be initiated. In polymyalgia, this dose will invariably produce a dramatic remission of symptoms and an increased sense of well being—at times within 24 hours. The steroid dosage may then be gradually reduced using the sedimentation rate and clinical symptoms as a guide. It may be necessary to treat with small amounts of steroids for 1 to 2 years before discontinuing therapy.

When headache, visual disturbances (transient blindness, diplopia, blurred vision), jaw claudication, or blanching of the tongue accompany symptoms of polymyalgia, giant cell arteritis should be suspected. In such instances, a temporal artery biopsy of adequate size (2 to 5 cm) should be serially sectioned in search for areas of round cell infiltration, the presence of giant cells, and disruption of the internal elastic membrane (Fig. 2). Steroids in the range of 60 to 80 mg of prednisone a day should be used initially in this condition. The incidence of large artery involvement in giant cell arteritis is greater than previously suspected. Klein[20] reported disease of the aorta or its major branches in 34 of 248 patients with giant cell arteritis. Symptoms included intermittent claudication of an extremity, paresthesias, and Raynaud's phenomenon. On physical examination, large artery pulses were absent or diminished, and bruits were heard over large arteries. Angiography was helpful in indicating arteritis rather than atherosclerosis in one third of the cases. Steroids in adequate doses produced a favorable response in most patients, with reduction of claudication and improvement of pulses.

POLYMYOSITIS

In contrast to polymyalgia, polymyositis is characterized by true muscle weakness. A rash may appear on the face, the V-line of the neck, or on the knuckles in about 30 per cent of cases. The diagnosis is established by a recognition of the clinical symptoms and signs: increased serum levels of SGOT, CPK, or aldolase, a myopathic electromyographic

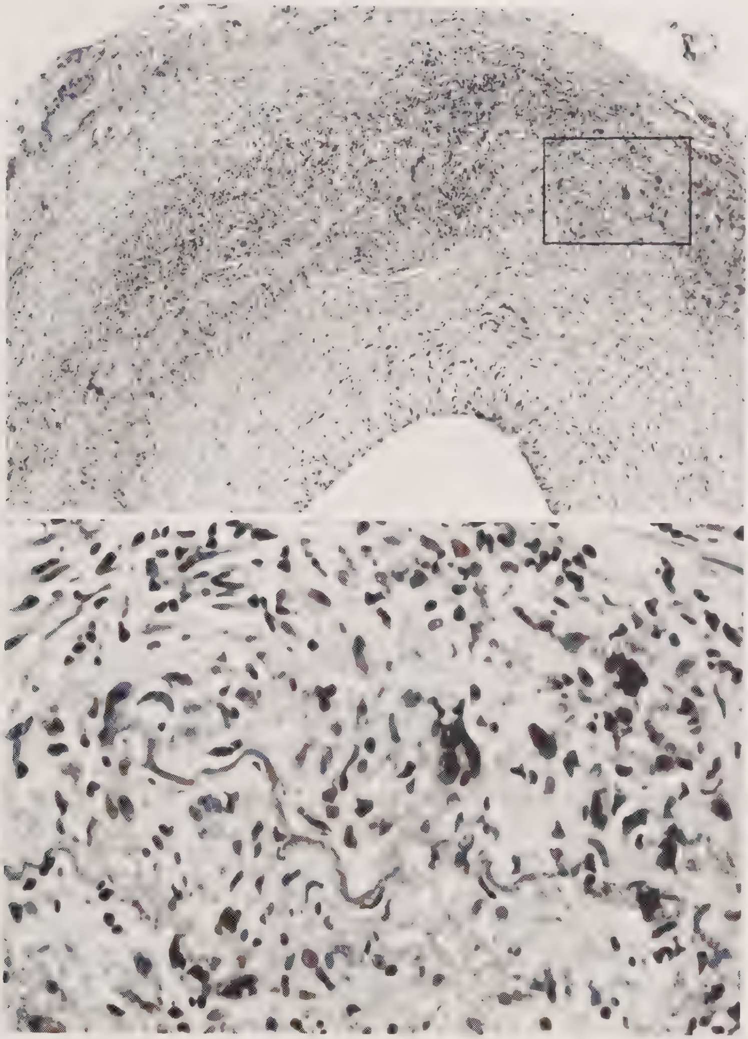

Figure 2. Cross section of temporal artery showing inflammatory cells in the media (×100). Higher magnification (*below*) reveals the presence of giant cells and disruption of the internal elastic membrane (×500).

pattern, and typical changes on an appropriately selected muscle biopsy. Treatment with high dosage corticosteroids (60 to 80 mg of prednisone per day) results in clinical improvement in one third to one half of patients. Methotrexate and other immunosuppressive drugs may be of value in patients who do not respond favorably to steroids, but this mode of treatment remains experimental.

The incidence of malignancy in polymyositis has been reported to be 5 to 7 times that of the general population.[1] The peak incidence of malignancy is during the sixth decade, tumors of the breast, lung, and ovary being most frequent. Most tumors were found within one year of the onset of polymyositis.

NON-ARTICULAR RHEUMATIC DISORDERS

The terms fibromyopathy, focal myalgia, trigger point, and fibrositis syndrome have all been used to describe a group of benign but painful disorders of muscle and connective tissue of varying clinical significance. In most instances, reassurance, treatment with local heat and massage, and the use of mild analgesic agents will result in improvement. Persistence of symptoms in the absence of clinical and laboratory evidence of underlying disease should alert one to consider the possibility of an underlying psychological disorder. Depression frequently expresses itself as a somatic disorder involving the skeletomuscular system in the elderly. A psychologic and social history will often bring into focus the source or sources of these varied somatic complaints.

Other non-articular disorders to be differentiated from polymyalgia rheumatica include calcific tendonitis and adhesive capsulitis. The latter condition, commonly seen in older people, may appear spontaneously or following trauma, hemiplegia, or pneumonia. Patients experience pain in the deltoid area and gradually increasing limitation of shoulder motion. On palpation, tenderness over the deltoid muscle is diffuse. Although the vast majority of patients with this condition have spontaneous remission in 6 to 24 months, a significant percentage are left with residual disability in spite of aggressive treatment. General measures including the use of analgesic agents, the application of moist heat, and range of motion exercises should be prescribed. Local installation of corticosteroids may be tried. Patients should be advised that it may take months for improvement of function to occur.

Shoulder-Hand Syndrome

A particularly painful and disabling condition is the shoulder-hand syndrome.[28] Ninety per cent of cases are seen past the age of 50. This disorder is characterized by shoulder pain and limitation and motion preceding or accompanied by stiffness, pain, swelling, and vasomotor changes in the hand. Symptoms usually begin in and around the shoulder, where weakness, pain, or limitation of motion may be present. The hand may be diffusely swollen for weeks to months. As swelling of the hand subsides, dystrophic changes, at times resulting in flexion contractures, may develop. Radiographic changes are absent at the onset, but patchy and later diffuse demineralization of the bones of the hand and wrist eventually occur. This condition has been associated with a variety of underlying illnesses, the most frequent being myocardial infarction, which precedes the syndrome in about 20 per cent of cases. Treatment is directed toward the relief of pain and inflammation and maintenance of joint motion. Analgesics and anti-inflammatory agents including systemic corticosteroids have been tried with variable success. Range of motion exercises for both shoulder and hand should be started as soon as possible. Stellate ganglion block has given relief to some patients not responding to medical therapy and exercise. Although prompt diagnosis and treatment improve the chances for recovery, 30 to 50 per cent of patients will be left with varying degrees of disability.

LABORATORY DIAGNOSIS

There are only a few instances in which the laboratory findings alone are specific enough to diagnose a rheumatic disorder. Many patients with inflammatory connective tissue disorders have a nonspecific anemia. Although rheumatoid factor is present in a vast majority of patients with rheumatoid arthritis it may also be found in a lower titer in a variety of other conditions. A rise in the incidence of rheumatoid factor and antinuclear antibodies in the serum in low titers has been reported to be associated with advancing age.[16]

Table 2 illustrates some of the characteristic laboratory abnormalities in blood and synovial fluid that may be found in various rheumatic disorders.

PHYSICAL MEDICINE AND REHABILITATION

An often neglected form of treatment is the physical and rehabilitative management of patients with rheumatic disease. It is here where the team approach to treatment—utilizing the services of internists, rheumatologists, physiatrists, orthopedic surgeons, therapists, and social workers—yields long-term dividends for the patient.

Initially, our main concern is directed toward the relief of pain and inflammation. As pharmacologic management progresses, our attention is directed to the maintenance and restoration of function of the affected area, and the achievement of functional independence consistent with physical and psychosocial limitations.

Many elderly patients who live alone manage to function adequately through habits acquired over a lifetime. When illness strikes, especially when mobility is affected, the patient's fears may surface. This frequently results in withdrawal and dependency. The "crippling" effects of arthritis and its resultant inactivity compound the sense of hopelessness. The attitude of the physician toward the patient and the disease can spell the difference between activity and independence and immobility and dependency.

General Principles of Therapy

The easiest and simplest physical measure employed during episodes of acute pain and inflammation is *rest*. This consists of general rest for the body and local rest of the affected joint(s) and extremity(ies) in particular. Local splinting, especially at the wrist, elbow, and knee, is most helpful in preventing development of flexion contractures. Except for hyperacute inflammation, for which cold ice pack applications may be useful for their numbing effect, moist heat is the most satisfactory and least expensive means of delivering heat to an affected area. Applications of hot towels, hydrocollator packs, paraffin baths, whirlpool, Hubbard tank, and pool therapy all have the general effect of delivering heat to the affected area. Moist heat relaxes muscle spasm and secondarily reduces pain. It facilitates improved range of motion and more satis-

Table 2. *Laboratory Diagnosis of Rheumatic Diseases*

	OSTEO-ARTHRITIS	RHEUMATOID ARTHRITIS	SPONDYL-ARTHRITIS	SYSTEMIC LUPUS ERYTHEMATOSUS	SCLERO-DERMA	POLYMYO-SITIS	GOUT	PSEUDOGOUT	SEPTIC ARTHRITIS
BLOOD									
CBC		Anemia		Anemia, leukopenia, thrombocytopenia					Leukocytosis
E.S.R.		↑	↑	↑	N/↑	↑	↑		↑
Latex fixation*		+80%		+20%		+30%			
ANA*		+14%		+98%	+25%	+30%			
LE Prep*		+10%		+75%					
SGOT		N/↑		N/↑	N/↑	↑			
CPK				N/↑	N/↑	↑			
Complement (serum)		N/↑	N/↑	↓			↑	↑	↑
SYNOVIAL FLUID									
Appearance	Yellow, transparent	Yellow to greenish cloudy	Yellow	Straw to cloudy	Straw	Straw	Yellow to milky cloudy	Yellow sl. cloudy	Grayish cloudy
Cell count									
WBC'S	1,000	15–25,000	1–50,000	5,000			10–12,000		80–200,000
Polys	25%	65–75%		10–50%			60–70%	25–50%	>75%
Complement		↓	↑	↓			↑	↑	↓
Crystals							( ) Bire-fringent	+) Bire-fringent	
Gram stain									+
Culture									+
HLA–27			(+) 60–95%						

*Reported results are variable.

factory performance of range of motion exercises. A note of caution is necessary—elderly and disabled patients may not be capable of preparing hot applications or paraffin baths. Accidents as a result of physical limitation or forgetfulness may lead to severe burns. Therefore a family member or aide should be instructed in the preparation and application of heat.

Exercise

Therapeutic exercises are used to restore motion and regain strength. The exercise program should be individualized, taking into account the patient's general health and exercise tolerance. Acute inflammation of the joint or surrounding soft tissues should have subsided before an exercise program is begun. Initial passive exercises should be followed by assistive, active, and finally resistive exercise. If the patient is immobilized in a cast or splint, isometric muscle setting exercises are useful to maintain muscle strength. In employing exercises in the elderly, one must be realistic. In many instances, exercise tolerance is severely reduced and longstanding muscle atrophy may limit treatment goals. The therapeutic program as outlined to the patient should be as simple to understand as possible. Diagrams, instruction sheets, and demonstrations are most helpful. The patient should be told to repeat the instructions and to demonstrate how he performs his exercises at subsequent visits. An appropriate balance between rest and exercise should be stressed.

As part of the overall program, patients should be taught to move each joint through its full range of motion, to avoid unnecessary strain on affected joints, and to use the strongest joints available for a given activity.

Assistive devices such as canes, crutches, walkers, and wheelchairs can be adjusted to the needs of the patient with the assistance of the physiotherapist and orthotist. A home visit by the therapist will help to assess the patient's future needs and to eliminate potential hazards. It is of little use to spend time and money teaching a program that cannot be carried out at home. Many assistive devices and appliances are available to alter the home for more efficient function. Again, the goal should be to achieve maximum independence within the constraints of the patient's illness.

ORTHOPEDIC SURGERY

The past decade has seen a revolution in the orthopedic surgical treatment of arthritis. That is not to say that surgical treatment is universally applicable or effective. The newer techniques have, however, offered a new lease on life to thousands of patients with degenerative joint disease and rheumatoid arthritis.

The physiologic status of the patient, rather than his chronological age, is the best guide to selection of patients. Synovectomy (the removal of diseased synovial tissue) may be considered for patients with persistent synovitis of the hands, wrists, or knees in whom pharmacologic and physical measures have not produced amelioration of the inflammatory process.

It is in the area of joint replacement that great progress has been made. Earlier procedures, including cup and hemiarthroplasty and arthrodesis, have been eclipsed by the total hip replacement or low friction arthroplasty. Here, the two joint surfaces are replaced by a metal and a high density polyethylene component which are fixed to the underlying bone with an acrylic cement (methyl methacrylate).

Advanced age is not a barrier to total joint replacement as long as the patient is able to withstand a major surgical procedure. The main indications for total hip arthroplasty are pain, limitation of motion, and joint deformity.[5] Any or all of these factors should significantly limit the patient's ability to function. Surgery should not be recommended in the presence of systemic or local infection. Overweight patients are less likely to have good results and should be advised to lose weight gradually before surgery is considered. In most series, over two thirds of patients undergoing total hip or knee procedures have been over 60 years of age. The excellent results obtainable in the case of the total hip replacement are illustrated in the 10 year follow-up of 185 low friction arthroplasties performed on 170 patients.[7] There were two postoperative deaths, three instances of loosening of the prosthesis, eight cases of sepsis and one case of unexplained pain for a complication rate of 7.4 per cent. The ability of this procedure to relieve pain and restore function in over 90 per cent of patients has been most gratifying.

The total knee arthroplasty results in considerable improvement of function in properly selected patients. It is best suited to treat the severely damaged, painful rheumatoid knee. Following this procedure, the patient usually requires a prolonged program of physical therapy. Recovery of function is usually slower and somewhat less satisfactory than following hip replacement. Patients with excessive bone loss or instability are poor candidates for this procedure. If only one compartment of the knee is involved, as frequently occurs in osteoarthritis, the condition may be managed by a more conservative surgical procedure, osteotomy.

Newer prostheses are being developed to replace shoulder, elbow, and ankle joints. It is too early to assess the value of these procedures.

CONCLUSION

If we reach old age, most of us will manifest some form of rheumatic disease. As has been outlined in this brief survey, our diagnostic tools are improving and our therapeutic armamentarium is becoming increasingly more effective. Amidst an array of tests, gadgets, and procedures stand the physician and his patient. Where modern science has been less than perfect, a compassionate heart, an attentive ear, and a hopeful attitude may stay the aches and pains—for yet another day.

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Rheumatology Division
Coney Island Hospital
2601 Ocean Parkway
Brooklyn, New York 11235

Diabetes in the Elderly Patient

*Bernard P. Shagan, M.D.**

Almost all physicians will agree that diabetes is an entity, the complications of which are varied and severe.[11] Progressive loss of function of the eyes and kidneys, involvement of the circulation, and nervous system lesions are the hallmark of this prolonged affliction and the chronic complications we all attempt to prevent. Yet if these same physicians were asked to define diabetes, their answers would vary markedly.[18] Indeed, there is no definition of diabetes which is universally accepted. The problems of definition become more and more troublesome as the age of the population under study increases. It is clearly recognized that both fasting and postprandial glucose levels rise progressively with advancing age.[1,12] Is this normally higher blood sugar usually found in older patients also normal from a pathophysiologic point of view? Can we base the diagnosis of diabetes upon the same criteria in the elderly as in the young?

What we are really asking are several basic questions about medicine's view of the diagnosis and treatment of the diabetic, namely:

1. Can we relate the level of blood glucose to the chronic complications of diabetes?
2. If we can, does this relationship apply at all ages or is it restricted to the younger patient?
3. Can we, by blood glucose measurements alone, identify those patients in whom the chronic complications of diabetes will develop?
4. Can we, by our treatment, stave off the long term ravages of diabetes?

The answers to these questions are not at all clear. Both in the literature[7-10,11,15] and among practitioners there is sharp disagreement about the relationship of control to complications. One conclusion of the University Group Diabetes Program (UGDP) which has not received wide attention is that the patients whose disease was better controlled had no fewer vascular complications than those whose disease was more poorly controlled. Every diabetologist has seen patients who have had poor control for years and have few, if any, chronic complications. On the

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*Chief, Division of Endocrinology and Metabolism, Coney Island Hospital; Assistant Professor of Medicine, State University of New York, Downstate Medical Center, Brooklyn, New York.

other hand, one can also readily find patients with recent onset of diabetes who have never had ketosis or seriously elevated blood sugar levels and yet who are already suffering from most of its major consequences. This disparity between blood sugar level and complications in the diabetic is particularly true in the older age groups, where "elevated" postprandial blood sugar levels are the rule rather than the exception. In many patients diabetes behaves as though its course were predetermined and as though there were little that we could do except prevent the acute metabolic problems: hyperosmolar coma, ketoacidosis, and hypoglycemia.

If we were able to help only a small proportion of our patients avoid the dire consequences of diabetes, we should be more than justified in treating them if the treatment did no harm. However, even the appellation, diabetic, may create the need for major changes in the patient's life. He must, if he is to be properly treated, adhere to a dietary program of greater or lesser rigidity, regulate and moderate his life, and receive regular medical care. One might argue that these changes are not necessarily harmful. On the other hand, the inability to obtain life or health insurance at reasonable cost can be a real problem. The need to change one's diet and perhaps to buy more expensive foods when one is on a fixed income is a worry to some patients. The specter of peripheral gangrene and blindness which hangs over the head of the "pronounced" diabetic certainly causes fear in the elderly patient who may have watched his parents, friends, and relatives fall victim to these dread complications. Therefore the physician should be quite sure he can accurately and specifically diagnose this entity before informing the patient that he has diabetes.

The University Group Diabetes Program,[13-17] while questioned by many experts in the field,[2,4,5] at the very least must cause concern about prescribing any oral hypoglycemic agent. With the wide publicity the results of the study have received, this concern is not only the physician's but the patient's as well. If it is true that oral agents caused more deaths from cardiovascular incidents than occurred in control patients having similar cardiovascular episodes, then we certainly must be far more circumspect in prescribing these drugs than in the past.

The biguanides (represented in this country only by phenformin) not only were found by the University Group Diabetes Program to increase the risk of death from cardiovascular disease, but also to cause major metabolic problems (see below) which place the elderly patient at particular risk.[19]

Insulin, the diabetic's life-saver, is also a two-edged sword. Regardless of the care with which insulin is prescribed and the careful regulation of the diet and activity of the patient, hypoglycemia is a risk which always attends its use. The risks from hypoglycemia are particularly great in the elderly. A typical sympathetic discharge is associated with rapidly falling blood sugar. It causes vasoconstriction, tachycardia, and a tendency for ectopic tachyarrhythmias and thus is a cause of myocardial ischemia and even infarction and sudden death. These events combined with the effects of low glucose upon the brain, sensitizing the brain to focal ischemia, lowering the seizure threshold, and causing direct cell damage and death, are the major consequences of insulin's acting in the absence of sufficient glucose substrate. The elderly patient with mild to moderate organic mental syndrome may well just forget to eat (or at least forget to eat on time). We have seen such patients who, having forgotten whether or not they took their insulin, took a second dose and arrived in the emergency room in deep coma. This type of occurrence is all too frequent in the elderly diabetic.

Furthermore, prescribing insulin for the elderly patient may well make the difference between his being able to live independently and his having to accept outside supervision of his life, or perhaps chronic institutionalization. Despite the availability of multiple aides for the handicapped patient, to help him draw up the correct amount of insulin and inject it properly, the nearly blind, forgetful, tremulous, and timorous elderly patient frequently is unable to perform these tasks and to avoid errors in dosage, missed injections, and improper injections. He may have to be supervised at home, or, as is usually the situation in our clinics, he will have to be hospitalized.

Because the treatment of diabetes is not free of risk to the patient and because there is no clear evidence that treatment abates, delays, or aborts the chronic complications of diabetes, especially in the elderly patient, we feel that the indications for initiating treatment with either oral hypoglycemic agents or insulin must be very clear before such therapy is used. These considerations, together with our experience in managing a diabetic clinic in which over half of the approximately 500 patients are over 60 years of age and an even older diabetic inpatient population, have led us to the following approach to the diabetic patient.

IN WHOM DO WE DIAGNOSE DIABETES?

We feel that the definition of diabetes must remain flexible in the elderly patient, and we cannot use the blood sugar alone in making this diagnosis. Patients with symptomatic diabetes (i.e., hyperglycemia with glucosuria, polyuria, polydipsia, weight loss, and polyphagia) are diabetic whether their fasting blood sugar levels are reasonably normal or not. Although the vast majority of patients above 60 years of age develop adult type diabetes (i.e., stable, relatively insulin-insensitive, ketosis-resistant diabetes), some do develop juvenile type diabetes (i.e. ketosis-prone, insulinopenic, unstable diabetes). Those in this latter group are clearly diabetic and require insulin, usually from the inception of their disease.

Patients who have peripheral complications of diabetes, such as retinopathy or neuropathy (including mononeuritis and meralgia paresthetica), will be called diabetic if their blood sugar levels, either fasting or postprandial, can be judged abnormal by any existing criteria—provided that no other cause can be found for the chronic complication. Patients who are normally euglycemic and asymptomatic, but who develop hyperglycemia and symptoms when placed on diabetogenic medications such as most of the oral diuretics (thiazides and related drugs, as well as furosemide and ethacrynic acid) or glucocorticoids will be considered diabetic. Patients with strong family histories of diabetes may be considered diabetic when their blood sugar levels are only 150 to 180 mg per dl, whereas those with no history might not be given this diagnosis.

WHAT IS THE TREATMENT?

We envision the treatment of diabetes as an equilateral triangle (Fig. 1). Changing the length of any side changes the level of blood sugar and thus the "control" of the diabetes. No side of the triangle is less important than any other in achieving stable control of the patient.

General Conditions of Living.

Foot care is especially important in the older diabetic in whom the diminished peripheral blood flow engendered by large vessel disease is added to the small vessel disease and neuropathy of diabetes to provide a near perfect setting for the development of limb and/or life-threatening infected ulcers and gangrene from even the most trivial injury to an extremity. Indeed, because of neuropathy, the patient may be unaware of the initial injury or the developing lesions. It is therefore imperative that the older diabetic be fully instructed in proper foot care, and that the physician closely examine the patient's feet each time he comes to the clinic. It is highly desirable to have podiatric care available for diabetic patients and for close liaison to be maintained between the physician

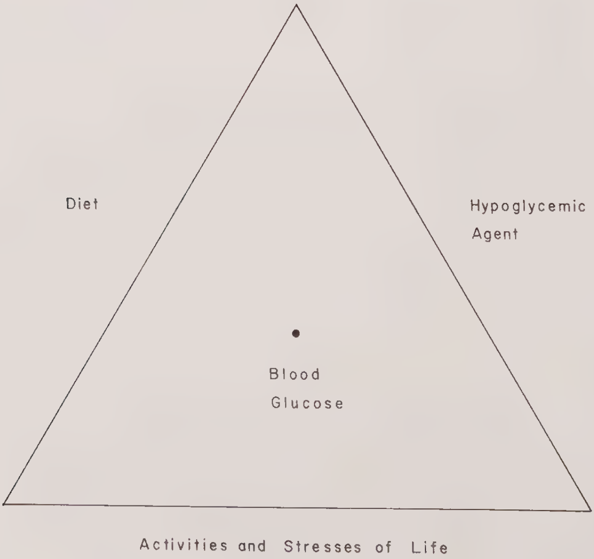


Figure 1.

and podiatrist treating these patients. We advise all hyperglycemic patients on proper foot care and continuously reemphasize the need for this care. The foot care instruction sheet which we use is shown in Figure 2.

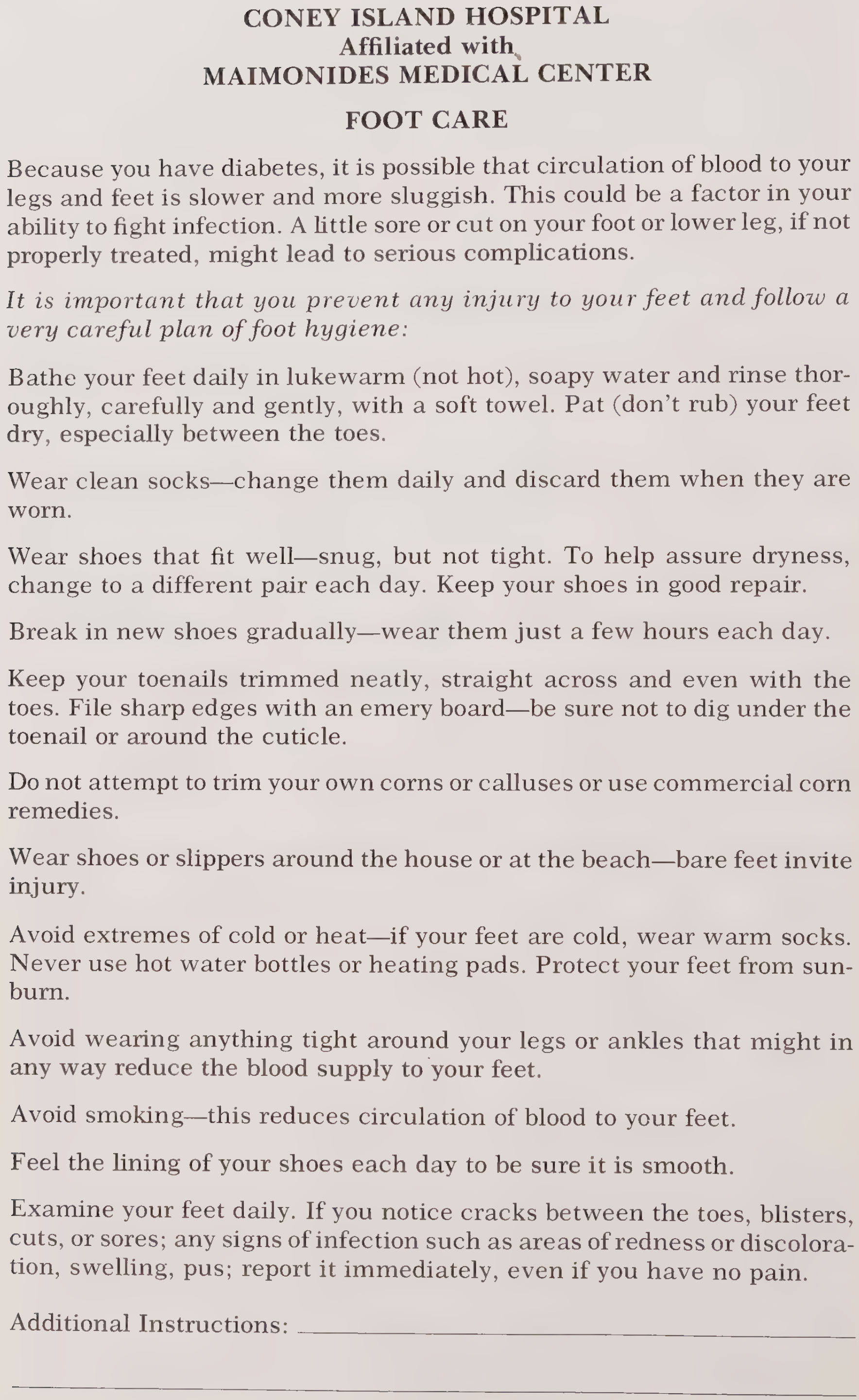
Muscular activity is one important way in which blood glucose can be lowered. Furthermore, adequate exercise allows increased caloric utilization and may permit the patient's diet to be somewhat less restricted. Yet in the elderly patient, exercise is frequently extremely limited by cardiac or peripheral vascular disease or by habit. It is important to encourage the elderly diabetic patient to do whatever exercise he can. Walking is excellent, and if the patient cannot walk long distances, we encourage him to take multiple short walks. The social and physical value of dancing should not be forgotten, and many of our older patients join senior citizens clubs where they can enjoy this activity. If exercise tolerance is so limited that no normal activities are tolerated, we attempt to set up a gradually increasing series of mild exercises in consultation with our physiotherapy department.

Like the younger diabetic patient, the elderly patient is subject to all the emotional stresses of living. Depression, anxiety, or feelings of helplessness may change his degree of control. His appetite may be diminished, or he may eat to compensate for his problems. Emotional stress in itself is a common cause of elevated blood sugar. One must treat the whole patient and not just his blood sugar level. Allowing the patient to talk, and discovering what is troubling him, may well prevent the physician from making changes in the therapeutic regimen which will be harmful when the acutely stressful situation improves.

There are few other diseases with as widespread effects on all organ systems as diabetes. On the other hand, there are few diseases which are so influenced by everything else happening to the patient. We should make every effort to avoid fragmented care of the diabetic. All decisions regarding therapeutic changes for the patient must be made in the light of full recognition of their effect on the diabetes. Thus, for example, the patient in whom congestive cardiac failure develops will require changes in the hypoglycemic regimen when he is placed upon diuretics. The patient who requires surgery may well need to be switched from oral hypoglycemics to insulin temporarily, and while he is unable to eat may require the provision of a regular carbohydrate intake parenterally. These are but two examples of the numerous situations in which the physician responsible for the diabetic must be involved in his total treatment.

Because of the frequency of urinary tract infection in the elderly diabetic, which may well be asymptomatic, we routinely obtain urinalyses and urine cultures annually. Some patients suffer recurrent urinary tract infections which repeatedly disturb control of their diabetes and may lead to sepsis. If investigations fail to reveal a correctable anatomic cause for these recurrent infections, we institute chronic suppressive therapy based on urine culture and sensitivity reports and on the patient's tolerance for the prescribed medication.

Another major threat to the elderly diabetic is loss of vision. Cataracts, glaucoma, and retinopathy are the major eye problems which



CONEY ISLAND HOSPITAL
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FOOT CARE

Because you have diabetes, it is possible that circulation of blood to your legs and feet is slower and more sluggish. This could be a factor in your ability to fight infection. A little sore or cut on your foot or lower leg, if not properly treated, might lead to serious complications.

It is important that you prevent any injury to your feet and follow a very careful plan of foot hygiene:

Bathe your feet daily in lukewarm (not hot), soapy water and rinse thoroughly, carefully and gently, with a soft towel. Pat (don't rub) your feet dry, especially between the toes.

Wear clean socks—change them daily and discard them when they are worn.

Wear shoes that fit well—snug, but not tight. To help assure dryness, change to a different pair each day. Keep your shoes in good repair.

Break in new shoes gradually—wear them just a few hours each day.

Keep your toenails trimmed neatly, straight across and even with the toes. File sharp edges with an emery board—be sure not to dig under the toenail or around the cuticle.

Do not attempt to trim your own corns or calluses or use commercial corn remedies.

Wear shoes or slippers around the house or at the beach—bare feet invite injury.

Avoid extremes of cold or heat—if your feet are cold, wear warm socks. Never use hot water bottles or heating pads. Protect your feet from sunburn.

Avoid wearing anything tight around your legs or ankles that might in any way reduce the blood supply to your feet.

Avoid smoking—this reduces circulation of blood to your feet.

Feel the lining of your shoes each day to be sure it is smooth.

Examine your feet daily. If you notice cracks between the toes, blisters, cuts, or sores; any signs of infection such as areas of redness or discoloration, swelling, pus; report it immediately, even if you have no pain.

Additional Instructions: ______________________________

____

Figure 2

are induced or worsened by diabetes and make it a leading cause of blindness. We have our patients seen by an ophthalmologist at yearly intervals if they have no ophthalmologic manifestations of diabetes, and more frequently if they do. Early treatment of glaucoma and laser therapy of retinopathy when indicated can prevent blindness. In patients who do have retinopathy, it is absolutely essential to control hypertension which increases the frequency and severity of bleeding from the newly formed, fragile vessels.

Little can be done to control the pain of diabetic neuropathy, which is typically severe, lancinating, and intermittent. The patient will frequently complain that this pain awakens him from sleep and that the only way in which he can obtain relief is by getting out of bed and walking around. Narcotic analgesics given at bedtime may permit the patient to have a few hours of uninterrupted sleep, but they should be given with extreme caution to the elderly patient. The pain may awaken him despite use of the analgesic and then he may experience confusion or vertigo as an effect of the drug. This may be worsened by the orthostatic hypotension so commonly found in these diabetics. The use of vitamin therapy (vitamin B_{12} or thiamine) has no greater effect than placebo in relieving this pain. Neuropathic pain is usually self-limiting. As the disease progresses, pain and sensation disappear. At this time the patient may experience episodes of falling due to loss of position sense and other sensation in the lower extremities. Some patients, not being aware of where they are placing their feet, complain of tripping over themselves. Braces which control foot drop and stabilize the ankle may be helpful in keeping these patients walking.

One should differentiate among the sharp lancinating pain of neuropathy which occurs either at rest or with activity, the pain of intermittent claudication which occurs only with activity, and the nocturnal leg cramps of unknown cause of which so many diabetics complain. These latter frequently occur just as the patient is awakening, or they awaken him. They are usually completely prevented by quinine, 300 to 600 mg given orally at bedtime. Diphenhydramine, 50 mg by mouth given the patient who is intolerant of quinine, will help prevent these cramps and may serve instead of a more potent sedative for the patient who is having trouble sleeping.

Diet

It has been aptly said that a diabetic diet is what a diabetic eats. There is probably no group of patients in which it is more difficult to influence diet than in elderly diabetics, who have set a pattern of eating for a lifetime and are very unlikely to be willing or able to comply with severe dietary changes. The following are some of the major problems in establishing the proper diet in this group of patients.

HABIT. Ethnic and social patterns of a lifetime exert major influence. Whatever diet is chosen must not conflict too greatly with these patterns or it will be rejected.

FINANCIAL PROBLEMS. Many elderly patients live on fixed incomes. As sources of protein become increasingly expensive, they are put out of reach of these individuals. Carbohydrate sources such as rice and bread have increased in price far beyond any increase in income for these patients. Whatever diet is chosen cannot be too expensive for the patient.

MEDICAL PROBLEMS. Because of other medical problems, patients frequently require diets with multiple restrictions. It is not unusual to find patients who are on sodium-restricted, low cholesterol, low animal fat diets who must now decrease their caloric intake and eliminate simple carbohydrates from their diet. Furthermore, many elderly patients cannot tolerate food that is difficult to chew. This multiplicity of dietary needs creates complex problems in prescribing a diet for these patients. Any diet prescribed may, of necessity, be extremely limited, and yet must meet the medical needs of the patient and provide adequate nutrition.

HOME RESOURCES. Many elderly patients living alone would prefer not to bother cooking. Their only hot meal may be a can of soup while for the rest of the day, they may nibble on such snack foods as are available. In urban areas they may prefer to bring in prepared food or eat in restaurants. They may have poor cooking or refrigeration facilities, preventing proper food storage and preparation. The patient must be able and willing to prepare any diet chosen for him.

COMPREHENSION. The elderly patient may have difficulty understanding a diet that is medically suitable yet designed to provide a relatively tasteful variety of foods. Even a simple, relatively unrestricted exchange type diet may offer so many choices as to be confusing to the elderly patient. The diet chosen may have to provide only limited choice so that it is simple enough for the patient to understand.

Along with these problems of the elderly, there are several problems specific to the diabetic patient that must be considered. The type and distribution of carbohydrate in the diet must be controlled if wide swings in blood glucose level are to be avoided. One common mistake in prescribing diets for these patients is the imposition of severe limitations on the amount of carbohydrate in the diet. This restriction may cause particularly serious problems in the patient receiving insulin, since it will frequently lead to episodes of hypoglycemia. Hypoglycemia stimulates the hormonal defenses of the body, and may cause rebound hyperglycemia (the Somogyi effect) and result in wide and frequent swings from hyperglycemia to hypoglycemia. Clearly these patients require that carbohydrate be in their diet and that it be eaten at times which allow its absorption to coincide closely with the peak effects of the insulin they are taking. To avoid wide swings in blood sugar, it is helpful to proscribe foods containing a large quantity of simple sugars. Most of the intake of carbohydrate should be in the form of starch, with simple sugars being provided by fruit. Milk is an excellent source of sugar, as well as of protein, but many elderly patients develop gastrointestinal distress with its ingestion because of lactose intolerance and therefore do not use it.

One need only consult a standard text on nutrition to see the multiplicity of opinions regarding the caloric need of patients and the ways to calculate this requirement.[20] Because there is a difference of opinion, and because the degree of activity of these patients is so variable, we take a pragmatic approach to caloric intake. The usual elderly diabetic requires between 1000 and 1500 calories daily to maintain his body weight at the relatively thin levels that are best for his diabetes and general health. If the patient is very active, very large without being obese, or catabolic, this may be increased. If he is very sedentary, small or obese, this should be decreased. We do not use diets of less than 600 calories per day because they can lead to too great a loss of nitrogen and potassium from the body, and represent a food intake so low that the ambulatory patient would find it virtually impossible to maintain.

There is little practical need to define obesity since in the vast majority of patients an excess of body weight will be quite obvious. If measurements are desired, we prefer a simple examination of the skin fold thickness over the arm, back and abdomen. An excellent description of the method used and its rationale may be found in reference 20 (pp. 21–22, 570, 975, and 1207). The use of standard weight tables to define obesity is also acceptable.

Having decided upon an approximate caloric requirement, and knowing which, if any, hypoglycemic therapy will be prescribed, we are prepared to begin writing the patient's diet. This is best accomplished together with the patient and anyone who usually cooks for him. First, a dietary history is taken, describing the patient's usual food intake (preferably specifying what he ate for each meal over the last few days). The patient's tastes in food, his concepts of portion size, and the hours at which he usually eats are discussed. If his usual diet provides the proper caloric intake and a protein intake of between 0.5 and 0.75 gm per kg per day, with the lower amount being required if adequate calories and high quality protein are consumed, the patient is told to remain on it. If there are problems in diet, a standard exchange program is used providing that the patient can understand it and enjoys the wide variety of food provided by the usual form of this diet. If not, a diet is prepared specifically for the patient that provides some choice from among his preferred foods at each meal, and specifies the amounts to be consumed. To this diet, if needed, are added whatever sources of protein or carbohydrate will meet the patient's requirements from among those foods that he will eat. Foods that he should not eat are specifically eliminated. Intercibal feedings are prescribed primarily to provide carbohydrates at those times dictated by his activity pattern and the characteristics of his hypoglycemic therapy. They may also be used to provide additional protein for the elderly patient who cannot consume enough at regular meals. If the patient's finances are a problem, specific advice should be given on lower cost protein sources, such as beans or fowl, or whatever is least expensive and acceptable to the patient. Fat is taken in the diet as part of the meat, cheese, and milk products prescribed. We attempt to keep the fat intake relatively low (less than 50 gm per day) and to suggest sources of unsaturated fats when additional calories are needed.

The diet prescribed at this time is not final. It is reviewed at subsequent visits in terms of the patient's acceptance, performance (i.e., weight loss or gain as required, hypoglycemic reactions, hyperglycemia), and feeling of well being. Modifications are the rule, not the exception.

It is important to stress that the diet used in the hospital setting is generally not appropriate for the patient at home since activity and time of eating will vary considerably from the usual hospital routine. We should again emphasize that the prescribed diet is pragmatic, based not only upon what is good for the patient, but also upon what he will eat and what he enjoys, insofar as that is possible. It is a diet that is within reach for the patient financially and which he has the facilities and mental capacity to prepare. When severe restrictions are imposed by medical, financial, or social problems, advice is given to help make the diet as acceptable as possible, but it will still be a limited diet.

The patient's comprehension of his diet should not be assumed. If he does not ask questions about it on the initial or subsequent visits, question him. There is no single ingredient more important to good control and a happy, comfortable patient than a good diet.

Hypoglycemic Agents

We try to restrict our use of oral hypoglycemic agents or insulin to those patients whose hyperglycemia is symptomatic and to those in whom hyperglycemia in itself presently or potentially represents a threat. Therefore if the patient's blood sugar level cannot be controlled adequately by diet and regulation of activities or when he presents with a blood glucose level so high that it must be lowered more quickly than could be accomplished by diet alone, the patient must be placed on hypoglycemic therapy. In the nonketotic patient, we consider that a blood glucose above 300 mg per dl, a progressively rising blood glucose level despite adequate dietary adherence, or the development of polyuria, polydipsia or weight loss because of uncontrolled sugar are absolute indications for such therapy. Such relative indications as the need to place the patient on diuretics or glucocorticoids, the patient's need for surgery, or the development of intercurrent infection must also be considered.

Thus the patient who normally is asymptomatic and has a postprandial blood sugar level of 200 to 250 mg per dl would probably not be placed on hypoglycemic medication for his blood sugar unless we noted that with mild infections (coryza, upper respiratory infections), dietary indiscretion, or other stress, his blood sugar rose significantly. The threat of hyperosmolar problems developing in these patients is real, and they require more than just diet for proper treatment.

Hyperlipidemic patients, even with minimal glucose intolerance, are treated with diet to normalize their blood sugar and serum lipids and may well be placed on sulfonylureas to modify the dyskinetic or increased insulin release so often found particularly in prebetahyperlipoproteinemia (types IV and V of Fredrickson).[6]

It should be noted that elderly diabetics usually have less glucosuria for a given blood sugar than younger diabetics.[12] This is true because they have lower glomerular filtration rates and thus higher renal thresholds for glucose. Therefore, elderly diabetics generally will not manifest symptoms related to glucosuria until their blood sugars are quite elevated. Furthermore, since their renal thresholds are high they have less ability to "escape" severe hyperglycemia by spilling excess glucose into the urine than do their younger counterparts. Their blood sugars will therefore tend to rise more precipitously and to higher levels than in younger diabetics who have normal or elevated glomerular filtration rates. Thus their blood sugars may be quickly driven to dangerously high levels by infection, stress, or high carbohydrate intake.

When the elderly patient is subject to a stress which raises his blood glucose and he experiences marked osmotic diuresis because of the consequent glucosuria, he may experience a loss of circulating plasma volume and consequently diminished glomerular filtration. This is accentuated if, because of illness such as stroke, high fever, and confusion, he is unable to replenish his fluid volume by drinking. Endogenous renal disease contributes to the problem. Serum levels of sodium and glucose rise dramatically as the blood volume contracts because of fluid loss, and less glucose and sodium are excreted because of diminished glomerular filtration. Yet the patient produces enough insulin to prevent massive lipolysis and ketogenesis. Because of these circumstances the elderly patient is particularly susceptible to the development of hyperosmolar nonketotic coma.

The most important aspect of treatment of these hyperosmolar states is replacement of the fluid volume which the patient has lost. If there is hypotension because of the hypovolemia, 0.9 per cent saline should be used initially to replace volume despite the patient's hyperosmolarity. If the patient is severely acidotic, as he may be, owing to increased lactic acid production from tissues deprived of normal circulation, sodium bicarbonate should be infused initially as an isotonic or slightly hypotonic solution. This can be achieved by mixing two or three ampules (each containing 44.5 to 50 mEq) of sodium bicarbonate in a liter bottle of distilled water, from which a volume equal to the volume of the bicarbonate solution to be added has been removed.

Except in the above circumstances, or when with treatment the patient has approached normovolemia, and severe acidosis, if present, has been treated, 0.45 per cent saline should be given intravenously until urine output is restored (without glucosuria acting as an osmotic diuretic) and the patient is no longer hemoconcentrated. It is not unusual to give 10 to 12 liters of fluid in 24 hours to these patients.

Insulin should be used very sparingly. Large intravenous doses can cause severe hypoglycemia in these insulin-sensitive individuals. We generally employ an initial dose of 10 U of crystalline insulin intravenously and carefully observe the response, which may be dramatic. The response to the initial small dose dictates further therapy. Subcutaneous insulin should not be used until the dehydration is completely corrected. Solutions containing glucose should be used only after the blood glucose has been brought to levels below 250 to 300 mg per dl. If intravenous glucose must eventually be used (because the patient cannot eat), care must be taken so that the entire sequence of hyperglycemia, osmotic diuresis, and dehydration is not reinitiated iatrogenically by this infusion.

There are three classes of hypoglycemic agents from which therapy may be chosen. These are insulin, the sulfonylureas and the biguanides.

Because of the difficulties involved in teaching the parenteral administration of insulin to the patient, the risks of hypoglycemia, and patient rejection of self-injection, the physician generally had opted for the use of an oral hypoglycemic agent prior to the publication of the University Group Diabetes Program study. With the announcement of these results, came the physician's fear that he might be harming his patients by increasing their risk of sudden death if he prescribed these agents, and that he might be liable if his patients should experience cardiovascular problems (which are so common in this age group) while taking them. Furthermore, with the wide publicity the results received, many patients have become resistant to taking these agents.

Because there is controversy regarding the validity of the University Group Diabetes Program results,[2,4,5] and other studies which have reached different conclusions,[3] we have not seriously altered our use of the sulfonylureas. Once we have decided upon the need for therapy, we choose it based upon the principles of expected benefits versus risks and disadvantages. We explain to the patient that oral therapy may be associated with a small increase in risk, and if he is capable of using insulin, or rejects the use of oral agents, we begin therapy with insulin. On the other hand, if he is resistant to using insulin, or if, as in many elderly patients, the previously noted disadvantages of insulin use tend to outweigh the expected benefits, we use oral hypoglycemic agents.

The mode of action of all the sulfonylureas seems to be the same. They increase insulin secretion by the pancreas, probably by increasing cyclic adenosine monophosphate levels in the beta cell. The side effects and toxic effects of the sulfonylureas are similar except for induction of the syndrome of inappropriate antidiuretic hormone (ADH) which has been associated almost exclusively with chlorpropamide use. This syndrome is probably more closely related to increased renal sensitivity to endogenous levels of ADH than to its excessive secretion. The frequency and severity of toxic effects seem to be directly related to the efficacy of the agent and its dose. Indeed the maximum suggested dose of each agent is the dose above which toxic effects continue to occur with increased frequency and significantly increased hypoglycemic effect is not seen. In Table 1 the sulfonylureas available in this country are listed together with their brand names, duration of action, and dosage information.

The major side effects and toxicities of the sulfonylureas may be seen in Table 2. Hypoglycemia may occur with any of these agents if it is used in excessive dosage, or when the patient's diet is improper. We have usually seen serious hypoglycemia only in the presence of renal or hepatic disease, or when the patient eats a meal consisting mostly of simple sugar without a more slowly absorbed carbohydrate source. This causes a marked output of insulin whose action is then unopposed by carbohydrate. The hypoglycemic effect of these agents may be intensified by a variety of other drugs such as aspirin, phenylbutazone, probenecid, bishydroxycoumarin, sulphaphenazole, sulfisoxazole, and monoamine oxidase inhibitors.

The biguanides are the second class of oral hypoglycemic agent. The

Table 1. *Currently Available Sulfonylureas*

GENERIC NAME	TRADE NAME	USUAL STARTING DOSE IF USED AS INITIAL THERAPY*	USUAL STARTING DOSE IF USED AS REPLACEMENT FOR LESS EFFICACIOUS AGENT	MAXIMUM RECOMMENDED DOSE (gm/24 HOUR)	DURATION OF ACTION (HOURS)
Tolbutamide	Orinase	0.5 gm b.i.d.	Not Applicable	2	6–8
Acetohexamide	Dymelor	0.25 gm daily	500 mg in A.M. 250 mg in P.M.	2	16–24
Tolazamide	Tolinase	0.1 gm daily	250 mg in A.M. 125 mg in P.M.	1	16–24
Chlorpropamide	Diabinese	0.1 gm daily	500 mg daily	0.75	36–48

*Aside from tolbutamide, we do not recommend initial therapy with these agents (see text).

Table 2. *Side Effects and Complications of Sulfonylurea Therapy*

- Hypoglycemia
- Cholestatic jaundice
- Rashes
- Hematologic complications
- Goiter (and possibly myxedema)
- Gastrointestinal symptoms* (usually mild): anorexia, abdominal pain, nausea, vomiting, or diarrhea
- Syndrome of inappropriate secretion of antidiuretic hormone**
- Possible increased cardiovascular mortality
- Disulfuram (Antabuse) effect

*Rarely require discontinuation of the drug
**Occurs almost exclusively with chlorpropamide

mode of action of phenformin most responsible for its therapeutic effects in human beings is not certain. It has been found to increase utilization of glucose due to a shift in metabolism from oxidative to anaerobic (Pasteur effect), decrease glucose absorption from the gut, and decrease gluconeogenesis in experimental animals. Toxic and side effects are common. Gastrointestinal effects are most common and range from a metallic taste in the mouth, anorexia and nausea to vomiting, abdominal pain and diarrhea which may be severe. We have noted a syndrome of general malaise, which when associated with diarrhea or other abdominal complaints, mimics viral gastroenteritis except for the absence of fever. Discontinuing the drug eliminates the syndrome. In contrast to the sulfonylureas, phenformin frequently induces gastrointestinal side effects severe enough to warrant its discontinuance. Because of the Pasteur effect induced by phenformin, which is very similar to the effect of exercise, not only does this agent induce increased glucose utilization, but, like exercise, it causes increased lactic acid production. This is its most dangerous toxic effect. In those patients prone to tissue hypoxia (e.g., patients with microvascular disease, heart failure, and ischemic heart disease), decreased pH or diminished clearance of the drug (e.g., patients with renal failure), or increased lactic acid production (e.g., patients who use alcohol), there is a significant risk of the development of lactic acidosis with its attendant high mortality. Because cardiac and renal disease is so common among the elderly, phenformin is strongly contraindicated in many of these patients. Furthermore, the literature describes,[18] and we have seen, lactic acidosis occurring in patients without precipitating or predisposing cause other than phenformin administration and diabetes, a fact which further limits the use of this agent.

The same increase in mortality due to cardiovascular disease imputed to tolbutamide has been noted with phenformin in the University Group Diabetes Program study and must also be considered before using this agent.

Following good pharmacologic practice, the least toxic agent which will fulfill the patient's requirements should be the first agent used. When this agent fails, the next most efficacious agent should be chosen. If a single agent is available which will do the job, there is no indication for combination therapy since the toxicities of two agents together are generally greater than the sum of the individual toxicities. Following these principles, we generally begin therapy with tolbutamide, if we have decided upon oral agents. The dosage used is 500 mg twice or three times daily before meals. This is increased until the patient's blood glucose levels are controlled. Our object is to bring the postprandial blood sugar to as normal a level as possible without causing hypoglycemia. Although drug therapy is not initiated until the blood glucose has risen significantly, once such therapy is started the risk to the patient is not increased significantly by using it to bring the blood glucose to the most normal level possible. Because of cost to the patient and the inconvenience of multiple doses, if he is not controlled at a dose of 500 mg three times daily, we switch to the next most efficacious agent, acetohexamide. The dosage level used here, as when switching from any oral agent to another or from insulin to an oral agent, is not the usual dose recommended for institution of hypoglycemic therapy, but higher than that. We begin with 500 mg in the morning and 250 mg at dinner. When there is lack of control at this dosage, this is increased to a maximum of 1000 mg twice daily. If at this point, good control is not achieved, either tolazamide or chlorpropamide is begun. If the patient has renal impairment, chlorpropamide, which is excreted by the kidneys without significant modification, carries too great a risk of being accumulated and causing hypoglycemia or other toxic effects. Therefore tolazamide is used starting with 250 mg in the morning and 125 mg at dinner, and progressing as needed to a maximum dose of 500 mg twice daily. It should be noted that to achieve continuous effect from tolazamide or acetohexamide, they should be given twice daily since the duration of their action is less than 24 hours. If the patient who fails on acetohexamide has no significant renal impairment, we choose chlorpropamide which should be given in a single daily dose of 500 mg. This may be increased to 750 mg daily, if needed.

In adjusting the dosage of these agents or changing agents, it should be realized that acetohexamide and tolazamide, when given twice daily, or chlorpropamide, when given once daily, take several days to reach the point of their maximum effective concentrations in the body (the point of biologic equilibrium where accretion is equalled by excretion and catabolism of the drug). Therefore if some immediate hypoglycemic effect is noted but is inadequate, we suggest waiting 3 to 5 days for the first two agents and 5 to 7 days for chlorpropamide before raising the dosage or changing the drug so that full effectiveness can be achieved without the risk of hypoglycemia. If no immediate effect on blood sugar is noted, the change may be made earlier.

We do not combine phenformin with either tolbutamide or acetohexamide since more efficacious sulfonylureas are available and can be used alone. If control cannot be achieved with tolazamide or chlorpropamide alone, we add phenformin in its timed disintegration form, 50 mg twice daily, if it is not contraindicated. If this combination does not achieve control, insulin must be used.

The only other circumstance in which we may employ phenformin is for the obese diabetic who requires more rapid lowering of blood glucose than diet therapy will permit and in whom we do not wish to use insulin or an insulin secretagogue because of the anabolic effect of these agents. Here we try to take advantage of the gastrointestinal side effects of phenformin, hoping that they will help our patient to decrease his food intake. Together with diet, phenformin in its short-acting form is used in doses of 25 mg two or three times daily, again with full awareness of its dangers and only when the patient's condition is clearly good enough from the cardiovascular and renal standpoints to tolerate the drug. When the patient has lost enough weight to control the blood glucose without added drug therapy, phenformin is stopped. This is usually quite soon and probably more related to decreased caloric intake than to weight loss per se.[8]

Insulin therapy is very much the same in the elderly diabetic as in the younger patient. For those patients who are visually handicapped or who have impaired manual dexterity, various aids are available to help with drawing up and administering insulin. These include a variety of pre-set syringes, gauges which attach to the syringe to measure the insulin, and automatic injectors. When the patient has difficulty filling the syringe but can inject himself, several days supply of disposable syringes may be prefilled with any single insulin or a combination of the Lente insulins and used as required.

Our aims in the older individual are to control symptoms that can be related to hyperglycemia, and keep the patient free of acetone and free of hypoglycemia. When these objectives are achieved, we attempt to bring the postprandial blood sugar to the most normal level possible while avoiding hypoglycemia. We generally find that in the elderly it is wise to start insulin in the hospital setting so that they can be taught to take it properly while diet and routine care are emphasized and hypoglycemia is watched for. We generally begin with a small dose of intermediate acting insulin (10 to 15 units of NPH or Lente insulin) and increase this until the late afternoon sugar is below 250 mg per dl. When this has been achieved, a small dose of rapidly acting insulin may be added to decrease late morning hyperglycemia, or a second dose of intermediate insulin may be used at night to control overnight and early morning glycemia. Addition of the second type of insulin or a second dose of insulin calls for re-evaluation of the afternoon sugar to be sure that overall glucose levels have not been lowered by the new insulin to a point where the morning dose of intermediate insulin is now causing hypoglycemia. A combination that we have found useful is Lente insulin together with a small dose of Ultralente insulin given in the morning.

While initial control should be established in the hospital, no attempt at close regulation should be made there. Hospital life is not the same as the patient's usual life in terms of activity, food, or emotional stress. We generally want the patient to leave the hospital without symptoms, but hyperglycemic. As close regulation as possible is accomplished with the patient living his normal life at home. Blood sugar levels probably should be allowed to remain higher in the elderly than in normal individuals or younger diabetics to avoid hypoglycemia and provide adequate glucose for cerebral metabolism.

PATIENT EDUCATION

Of all the things we do for the diabetic, we regard his education as most important. The non-institutionalized diabetic must care for himself most of the time. Although close contact with the patient is maintained by telephone and frequent clinic visits, he still must be responsible for his own care. Therefore we direct a major effort toward teaching all our patients, or family members, as much as they are capable of learning about diabetes, its physiology, complications, and treatment. We teach urine testing, foot care, and diet as well as insulin administration when required. There is no medical entity requiring as close cooperation between physician and patient and as much work for as long a time as diabetes. We have no right to expect the diabetic who has not been properly trained to perform his part of the job.

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Division of Endocrinology and Metabolism
Coney Island Hospital
2601 Ocean Parkway
Brooklyn, New York 11235

Is Diabetes a Model for Aging?

*Bernard P. Shagan, M.D.**

In the previous article we presented a pragmatic clinical approach to the treatment of diabetes in elderly patients. Another relationship between diabetes and aging has become increasingly apparent. Among younger diabetics a variety of degenerative diseases, including peripheral arterial disease, arteriosclerotic heart disease, stroke, senile cataract, osteoporosis, osteoarthritis, periodontal disease and premature loss of teeth, tendonitis, bursitis and loss of vibratory sensation in the extremities, occur earlier and with greater severity than among their nondiabetic peers.[1,7,10] Thus in many ways the younger diabetic seems to age more rapidly than normal. Two questions regarding this apparently accelerated aging are a basis of controversy:

1. Are the changes observed truly the same as those seen in aging?
2. What is the relationship between control of the blood sugar and these changes?

While the answer to the first question will have to await a much more precise biochemical and pathophysiologic definition of the changes of aging, the second question has been extensively studied. Although no resolution of this controversy is yet possible, several studies indicate that hyperglycemia, by itself, cannot be responsible for all the degenerative changes found in the diabetic.

Many studies have pointed out that diabetic patients may have vascular changes in large arteries occurring years before they develop carbohydrate intolerance.[2,3,5] In studies of overtly diabetic subjects, no correlation has been found between the degree of carbohydrate intolerance and the severity of vascular changes. In one study of arterial pulse waves in diabetic children, Pillsbury et al.[8] report, "These changes in pulse wave velocity and contour are associated with increased wall stiffness that occurs with aging and suggest that the large arteries of diabetic children may exhibit acceleration of the aging process." Several authors have pointed out the high incidence of arteriosclerotic heart disease in patients with very mild diabetes. In an editorial in the American Heart Journal, Scott[10] points to lipid abnormalities related to hyperinsulinism as a possible etiologic consideration in the development of premature coronary artery disease in mild diabetics. A similar view is expressed by Reaven and his colleagues[9] who noted that development of hyperinsulinism without hyperglycemia in diabetic patients with mild glucose intolerance fed a balanced formula diet. They suggest the need for controlling hyperinsulinism in these patients.

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*Chief, Division of Endocrinology and Metabolism, Coney Island Hospital; Assistant Professor of Medicine, State University of New York, Downstate Medical Center, Brooklyn, New York

Degenerative diseases developing in a patient with diabetes could be caused or influenced either by genetic abnormalities in the patient or by metabolic abnormalities, or by both. In studies of the intact individual, it is impossible to separate these influences. In 1969, Goldstein et al.[4] demonstrated that fibroblasts cultured from the skin of the "prediabetics" and patients with minimal glucose intolerance behaved in much the same manner as senescent cells. In this study, cells taken from patients with no demonstrable abnormality in glucose metabolism or insulin secretion showed less ability to survive reculturing than cells taken from normal controls of the same age group. Thus a defect in cells other than the beta-cell and unrelated to abnormal metabolism was demonstrated in patients with a strong family history of diabetes.

If this same premature aging of cells occurs in vivo, it could account for many of the abnormalities observed in diabetics. Premature loss of both endothelial cells and pericytes in the retina might be primary defects leading to further changes of diabetic retinopathy, rather than changes secondary to abnormal glucose metabolism. The same type of mechanism could be operative in small vessels throughout the body leading to other manifestations of microvascular disease in diabetics. Endothelial cell loss could also be the initial large blood vessel injury leading to atherosclerotic plaque formation in these patients. Clearly, if premature senescence of cells is a generalized phenomenon in diabetics, its relationship to the degenerative disease found in these patients must be considered.

Collagen normally changes its characteristics with age. Taking advantage of the increased stability of aging collagen, Hamlin et al.[6] have described a method for determining the age of patients by measuring the digestibility of their collagen. Collagen from the three juvenile diabetics in their study showed markedly decreased digestibility when compared to collagen from normal individuals of the same age, and according to their standard curve showed a determined age 50 to 60 years greater than the patients' actual chronological age. Whether this change is true accelerated aging or not cannot be determined with certainty, but it is clear that this collagen behaves as if it were old. If such changes can be demonstrated in patients with mild diabetes or in prediabetics, the argument for a genetic cause of the degenerative lesions of diabetes unrelated to glucose metabolism will be stronger.

Patients with diabetes do not show early aging of all their organs and tissues. Yet in many ways they do experience the diseases of aging prematurely. If they experience these changes because of their abnormal glucose metabolism, much greater effort must be made to develop methods for continuously controlling blood glucose (such as beta cell transplantation or an artificial mechanical pancreas). On the other hand if these changes are true manifestations of premature aging, the emphasis of research and treatment will have to be totally different. Indeed, if diabetes is a model of aging, the changes occurring in diabetics may be useful for studying aging in general.

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Coney Island Hospital
3601 Ocean Parkway
Brooklyn, New York 11235

Osteoporosis

*Mary Wheeler, M.D.**

Osteoporosis, like arteriosclerosis, is almost universally found in the elderly. Like arteriosclerosis, it develops insidiously over a period of many years and once it has become severe, finds clinical expression either as a sudden, devastating event or as a chronic, painful condition. Despite these similarities, osteoporosis lacks the charisma of coronary disease. This is partly because it is not associated with the sudden death of a young breadwinner but also because it has been poorly understood, involves an organ with which many internists are unfamiliar, and because at present, no highly successful therapy is available.

In this article we will discuss some of the elements of bony structure and function, the differential diagnosis of osteoporosis, some of the treatments which have been proposed, and the prevention and management of some of the complications of osteoporosis.

NORMAL BONE STRUCTURE

Normal bone is usually referred to as a living tissue, but in the strictest sense this is only partly true. For although all normal bone contains an abundance of viable cells which are metabolically active, the part of bone having the most functional significance to the living organism is composed of proteinaceous secretions of these cells in which a large amount of inorganic matter has been deposited. Thus the *noncellular* components of the skeleton are responsible for the strength and rigidity of the bones, and also serve as the body's largest mineral reserve. Nevertheless, the skeleton is the *product* of cells, and since it remains under the influence of these cells and is consistently being renewed, the nature and function of the living component of bone is also of importance in the study of osteoporosis.

In the adult, bone is formed in a succession of layers. These layers, or lamellae, are formed sequentially by osteoblasts. As they are formed, a number of osteoblasts remain within each layer, become entrapped within the bone, and are transformed into osteocytes, the metabolically active cells of "resting" bone. Each set of lamellae is arranged so that the living cells remain in relation to a blood supply. In spongy, cancellous bone such as is found in vertebral bodies, the ribs, or at the diaphysis of long bones such as the femur, these lamellae form spicules which remain in direct contact with the marrow cavity. In compact or cortical bone, lamellae are laid down concentrically around a central arteriole, forming a haversian system. Each set of lamellae (or haversian system) forms a metabolic unit. The cells which are embedded within the bone maintain contact with each other by means of fine cellular processes which extend into the bone. This web-like system of cellular filaments accounts for the ability of bone to react as a metabolic unit.

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*Associate Chief of Endocrinology and Metabolic Division, Coney Island Hospital; Assistant Professor in Medicine, State University of New York, Downstate Medical Center, Brooklyn, New York

The first part of new bone to be formed by the osteoblasts is the organic phase, the matrix or osteoid. Matrix contains a variety of glycoproteins and mucopolysaccharides but is composed mainly of collagen. The shape taken by the collagen directs the shape of the bone to be formed. Collagen is the basis for much of the strength of bone, and is the framework on which the minerals are deposited. Of all proteins, it is unique in that it contains the aminoacids hydroxyproline and hydroxylysine in high concentrations—about 10 per cent and 0.5 to 1 per cent respectively. Collagen is secreted by the osteoblasts as three peptide chains which are twisted together (procollagen). A small fragment separates from one end of the procollagen helix after it is secreted by the cell and tropocollagen units are formed. These units then polymerize. The polymerization occurs in staggered units of equal spacing and results in the typical cross-striated appearance of the collagen fibers on electron microscopy. Collagen subsequently undergoes some more complex structural changes which are not as well understood but which include linkage between polymerized units. These changes are collectively known as maturation.

The mineralization of matrix is a complex process which is influenced by several factors. Calcium is deposited in bone both as amorphous calcium phosphate and as crystalline hydroxapatite ($Ca_{10}(PO_4)_6 \cdot (OH)_2$). Much of the initial mineralization occurs in relation to the collagen and the crystals are thought to be located between the individual collagen units, within the "gaps" formed by the staggered arrangement and also in the interstices of the fibrils. In the later phases of mineralization, crystals are formed in the matrix between the collagen fibrils. The mineralization is responsible for the rigidity of the bone and is presumed to be more or less continuous since, if collagen is completely digested from bone in vitro, the shape of the bone is preserved.

Mineralization was originally thought to occur solely as the result of physiochemical processes—precipitation occurring whenever the solubility product of calcium phosphate was exceeded. Mineralization of collagen can be demonstrated in vitro using collagen from any source and solutions of calcium phosphate. However, collagen in tendons and fibrous tissue does not normally calcify. Even in bone, there is a period of 8 to 10 days after collagen is formed before calcification begins. Protein-polysaccharide substances in immature matrix and in tendons may be responsible for inhibiting calcification, but the mechanism is unknown. The osteocytes also play an active role in mineralization, the mitochondria being involved in the transfer of calcium and phosphates into the matrix.

After a variable period of time—often years, in the adult—normal bone is renewed by a process known as remodeling. Through the action of multinucleated cells (osteoclasts), both organic and mineral phases of the bone are reabsorbed in a sharply localized area and then replaced, by osteoblasts, with a new metabolic unit. The nature of remodeling is such that the portion of bone resorbed does not correspond to a previously formed set of lamellae but may overlap two or more previously existing metabolic units. Since no cellular debris is found in bone which is being remodeled, it is felt that the same cells assume, in sequence, the roles of osteoblast, osteocyte, osteoclast, and again osteoblast. Thus, the same cell which is responsible for the formation of bone continues to be metabolically active in intact bone and ultimately is responsible for its dissolution, only to immediately undertake the creation of new bone.[16] Furthermore, the potential to derive new lines of osteoblasts from undifferentiated cells is retained throughout life and is regulated by a substance or substances found in bone matrix.[14] During the process of remodeling, collagen is cleaved and the resulting peptides are not recycled. The presence in the urine of hydroxyproline thus reflects the extent of bone resorption.

DIAGNOSIS

Osteoporosis is a condition in which the total skeletal mass is decreased, but the shape, composition, and morphology of bone are normal. It is distinct from osteomalacia, which is characterized by the presence of uncalcified matrix (osteoid) and in which abnormal or defective mineralization occurs. Although osteoporosis is widespread in the elderly, diagnosis is seldom made in the early stages because small changes in bone structure are difficult to detect radiologically. Therefore, recognition of the condition is often delayed until a fracture occurs.

Since much of the disability of osteoporosis results from vertebral osteoporosis, a direct measure of vertebral mineralization would be desirable. But the human condition allows for so much variation in soft tissue mass that x-ray films of the spine have not been found to be a reliable guide to the diagnosis of osteoporosis. Double-blind studies of the diagnosis of osteoporosis using plain films of the spine have shown major inconsistencies in interpretation of sequential films by the same radiologist, related to minor variations in positioning and exposure.[9] Bone biopsy, a technique which has occasionally been used experimentally for the assessment of osteoporosis, cannot be considered either a routine or a benign procedure and, like radiographic techniques, cannot ordinarily be used to evaluate the vertebral bodies. Because of these limitations, attempts have been made to develop more accurate measures of bone density. Most of these methods have used some portion of the appendicular skeleton where the ratio of soft tissue mass to bone is low. Even greater accuracy can be attained by measuring the absorption of monochromatic radiation such as is emitted from certain radioactive isotopes. A number of techniques have been developed for determining bone density of the radius, calcaneus, or a digital phalanx using an isotope source,[10,18] usually ^{125}I. Although these techniques hold some promise, they do require specialized equipment and the findings may not always reflect the state of the bones of the axial skeleton.

Calcium balance studies have been carried out in an attempt to document calcium losses and monitor response to therapy of osteoporosis. Most dietary calcium is excreted in the feces in amounts of about 600 mg daily. Accurate balance studies also require measurement of urinary calcium losses, which are smaller but which may introduce additional errors. Dietary calcium, even if supplied as a formula feeding, may also be inexact. Over a period of 20 years, a net loss of only 30 mg per day would result in the disappearance of one third of the total skeletal calcium. These studies suffer in design because the methods are not able to reliably detect such small variations since differences in stool collection times introduce large errors.

A reliable determination of total body calcium ought to be a dependable measure of osteoporosis since 99 per cent of the total body calcium is skeletal calcium and since, by definition, skeletal calcium in osteoporosis is lost in proportion to bony mass. Unfortunately, most skeletal calcium is not readily exchangeable, and isotopic dilution studies measure only the fraction of skeletal calcium—variously estimated but probably 1 per cent or less—which is either at the surface of a crystal, or which happens to be released as a result of normal bone remodeling. Isotopic balance studies are further limited by the necessity for measuring fecal calcium losses over a relatively long period of time, and by the amount of radioactive calcium which can be safely administered.

Attempts have been made to measure total body calcium by neutron activation analysis.[6] Neutrons will transform one of the stable isotopes of calcium into calcium^{49} which emits gamma radiation and has a half-life of 8.8 minutes. This technique has no clinical usefulness because it requires a cyclotron to generate neutrons and because the amount of radiation the patient receives is quite high. It is significant mainly because it is the best standard available to correlate with other means for appraising skeletal mass.

The definite diagnosis of osteoporosis, therefore, is usually made either in advanced disease, or else is inferred by the presence of fractures, especially fractures with minimal trauma, vertebral compression, or characteristic vertebral deformity ("dowager's hump") often associated with back pain. Hip fractures, although usually traumatic, are frequently used as an index of osteoporosis in a population because they seldom occur in the absence of osteoporosis.[2,12] (Young adults are more subject to fractures of the pelvis or femoral shaft, or to hip dislocations).

PATHOPHYSIOLOGY

Since no specific defect in the cellular elements, the matrix, the mineral components, or the structural arrangement of bone has ever been demonstrated, osteoporosis is presumed to result from an imbalance, usually over a long period of time, between the two aspects of bone remodeling, resorption, and formation. Many factors influence bone remodeling. These include many of the hormones, and also a variety of dietary, environmental, and constitutional factors. Many of these agents have known actions on bone resorption or renewal. Some of them are responsible for special forms of osteoporosis, and a differential diagnosis of osteoporosis can be derived from these. Other factors are associated with protection against the development of osteoporosis and many have been used in treating osteoporosis as well.

Parathormone

Parathyroid hormone has dominated thinking about bone physiology for the past 30 years. Parathyroid hormone stimulates both osteoblastic activity (new bone formation) and osteoclastic activity (bone resorption) but its major effect is on resorption. Parathormone action on bone cells is mediated by cyclic AMP, and the immediate effect is the uptake of calcium from the bone by osteocytes. Bone resorption by osteoclasts does not begin immediately; differentiation of osteoclasts is seen about 24 hours later. Thus, minor or transient elevations in parathormone levels result in a change in the metabolic activity of the "resting" bone units to supply small amounts of calcium for fine regulation of mineral homeostasis, whereas greater or more prolonged elevations would activate mechanisms capable of supplying larger amounts of calcium.[16] The original observation that hypocalcemia stimulates and hypercalcemia inhibits parathormone secretion has been confirmed many times. Present evidence points to serum calcium levels as the primary—possibly the only—stimulus for the regulation of parathormone secretion.

Hyperparathyroidism is not an uncommon disorder in the elderly and is often accompanied by osteoporosis. Since the advent of multiphasic screening, many more cases of asymptomatic hyperparathyroidism in the elderly have been identified. The management of such patients presents a problem because of the frequent coexistence of cardiovascular disease, the increased risk of surgery, and the reluctance of the elderly to consent to surgical therapy for an asymptomatic disorder. The policy at Coney Island Hospital over the past 10 years has been to defer surgery in patients over the age of 70 if there are no demonstrable renal, osseous, or gastrointestinal complications, if the patient is willing to return for periodic follow-up, and if the serum calcium is only minimally elevated (less than 11.0 mg per 100 ml most of the time). Of 20 such patients, 2 were subsequently subjected to surgery because of rising serum calcium levels and recovered uneventfully, and no patient has developed complications attributable to the hyperparathyroid state. Prolonged follow-up of these patients will be required before a full evaluation of the risks of nonoperative treatment of mild hyperparathyroidism in the elderly can be made.

Vitamin D

Vitamin D is another important regulator of bone physiology. Man can synthesize vitamin D in the presence of sunlight, but usually he must supplement his diet to satisfy his needs. Vitamin D_3 is hydroxylated at the 25 position in the liver and at position 1 in the kidney; the product, 1,25-dihydroxycholecalciferol, is now felt to be the biologically active metabolite. It markedly increases the active transport of calcium by the intestine which is required for efficient absorption. It also appears to be required in order for parathormone to exert its effects on the bone and on the kidney. Vitamin D intoxication results in hypercalcemia but ordinarily not in bony rarefaction. Vitamin D deficiency causes bony demineralization characterized by a disproportionate amount of matrix and wide layers of osteoid. Because parathormone-mediated bone resorption is inhibited, calcium stores are not available for recycling. Since neither dietary calcium nor bone calcium can be used, mineralization of osteoid is impaired. Vitamin D is therefore unlike parathormone in that no clinical disorders with which it is associated lead to osteoporosis. When the diagnosis of osteoporosis is based on microscopic examination of bone, vitamin D deficiency states can be excluded. But when the diagnosis is made radiologically, the differential diagnosis between osteoporosis and osteomalacia is often impossible. In clinical practice, therefore, all of the causes of vitamin D malabsorption and deficiency must be considered in the differential diagnosis of osteoporosis.[1]

Other Hormonal Agents

The incidence of osteoporosis is greater in women than in men, and osteoporosis is often seen at an early age in women with early menopause. These observations are so striking and consistent that the word "postmenopausal" is often used as a descriptive term for osteoporosis in general. Both population surveys and serial studies of bone density have shown an acceleration of bone loss after menopause. Estrogen has been shown to inhibit bone resorption[17] but its mechanism of action is unknown.

Early clinical descriptions of Cushing's syndrome noted the presence of bony rarefaction and vertebral compression fractures. The induction of osteoporosis by adrenal cortical steroids is of some importance because adrenal cortical hyperfunction must be considered in the differential diagnosis of osteoporosis, and also because steroid-induced osteoporosis is an important and serious complication of steroid therapy, especially long-term steroid therapy. Glucocorticoids inhibit the intestinal absorption of calcium, and increase bone resorption. A slight increase in parathyroid activity, compensating for the decreased intestinal calcium absorption, may be the cause of this increased resorption. Additionally, the formation of matrix may be inhibited by the general protein catabolic effects of steroids.

Hyperthyroidism is regularly associated with increased calcium excretion and with osteoporosis. Both bone resorption and bone formation are markedly increased in hyperthyroidism, but resorption is greater and may result in hypercalcemia. This seems to be a direct effect of thyroid hormone, similar to its metabolic effects on all cells.

Osteoporosis occurs in patients with acromegaly, but the mechanism is not clear. It has been attributed to the hypogonadal and hyperthyroid states sometimes seen in acromegaly, but osteoporosis occurs even in patients who do not show these features. Since acromegaly is uniformly associated with active periosteal bone formation, one theory holds that new cortical bone is formed at the expense of trabecular bone when calcium supplies are limited. The osteoporosis which results is, in fact, seen chiefly in trabecular bone, but further understanding of bone metabolism in acromegaly will have to await the development of new concepts of the mechanisms of growth hormone action on bone.

Mechanical Factors

One of the most interesting and puzzling causes of osteoporosis is immobilization. Patients with paralytic polio were often seen to resorb bone so rapidly that symptomatic hypercalcemia ensued; however, even partial immobilization results in bony loss. Localized osteoporosis is often associated with hemiplegia, fractures, and severe arthritis; prolonged bed rest may lead to generalized osteoporosis. Calcium loss has also been demonstrated as a result of weightlessness in astronauts during space flight. Obesity, which places increased mechanical stress on bones, is associated with a decreased risk of osteoporosis.[7] The mechanisms which relate physical stress to bone remodeling are largely unknown. The most attractive theory is that mechanical stresses set up local electrical charges, and that the ion fluxes or membrane potentials in some way provide the signal for new bone formation.

Diet and Osteoporosis

Osteoporosis has been related to dietary factors.[13] (In this respect also, it resembles atherosclerosis.) Estimates of the dietary intake of calcium by adults fall far short of the 800 mg per day recommended by the National Research Council. Table 1 lists some of the foods containing relatively high levels of calcium. If few dairy products are consumed, a diet chronically deficient in calcium but relatively well balanced in all other respects can be maintained for years. Calcium deficiency over a period of many years could conceivably result in osteoporosis, especially since the expected consequence of calcium deficiency would be chronic, low-grade hypersecretion of parathormone.[14] This theory, although attractive, has been contested[1] because of the known inaccuracies of retrospective dietary surveys, and because women with minimal osteoporosis have dietary habits which do not differ markedly from those of women with severe osteoporosis.

A second theory relating diet to osteoporosis is based on the fact that hydroxyapatite contains basic groups. These groups serve as a buffer and might be selectively reabsorbed in chronic acidosis. Administration of acid-containing diets, has, in fact, been observed to result in an increased urinary excretion of both calcium and hydroxyproline.[2] Long-term administration of ammonium chloride to animals results in osteoporosis. Parathyroidectomized animals do not tolerate acid loads well, and the effects of acid-loading on calcium balance are presumed to be mediated through parathyroid hormone. Since most dietary acid is derived from meat and poultry, this theory is consistent with the observation that osteoporosis is more prevalent in developed countries, where

Table 1. *Foods Containing High Amounts of Calcium**

FOOD	QUANTITY	CALCIUM (MG)
Milk, whole	1 glass	288
Bread, white, with calcium propionate added	1 slice	24
Cake, white, from mix	1 oz slice	33
Corn muffin, or muffin made from mix with calcium propionate added	one	60
Home made muffin, not corn	one	21
Cheese, creamed cottage	½ cup	118
American process cheese	1 tbsp	116
Leafy vegetables:		
Mustard greens, cooked	¼ lb	156
Rhubarb, cooked	¼ lb	87
Turnip greens	¼ lb	205
Kale	¼ lb	208
Spinach	¼ lb	104
Collards	¼ lb	209
Nuts		
Brazil nuts	1 oz	53
Almonds	1 oz	66
Filberts	1 oz	59
Peanuts (without skin)	1 oz	17
Fish		
Herring, canned, solids and liquid	3 oz	125
Sardines, canned (Atlantic)	3 oz	369

*Adapted from: Composition of Foods, Agriculture handbook No. 8, United States Department of Agriculture, 1963.

more protein is consumed. Since osteoporosis is also more common in Caucasian Americans than in Black Americans, genetic factors may predispose to or protect against osteoporosis. Studies using a variety of techniques consistently show that Black individuals have denser bones than whites of the same age and sex. Hip fractures, which are seldom encountered in the absence of osteoporosis, are at least ten times more common in white women.[5]

Other Causes

Osteoporosis has been reported to occur in a variety of other conditions. The most important of these, clinically, are diseases in which neoplastic infiltration of bone simulates the radiographic appearance of osteoporosis. Patients with multiple myeloma, in particular, often have such x-ray findings. Recently, bone-marrow and lymphoid cells from patients with myeloma have been shown to secrete a soluble material composed wholly or partly of protein. This substance stimulates osteoclasts and has been designated osteoclast-activating factor (OAF).[15]

Heparin has been shown experimentally to increase bone resorption, and long-term administration of heparin to both experimental animals and human beings has been reported to cause osteoporosis, pathologic fractures, and delayed fracture healing. Since mast cells produce heparin, it is significant that osteoporosis occurs in systemic mastocytosis. Here the osteoporosis may be localized and, when it is, it tends to occur in those areas with the greatest numbers of mast cells.[2]

Prostaglandins have recently been shown to affect a wide variety of biological processes, and bone remodeling is no exception. PGE_1 and PGE_2 have been shown, in tissue culture, to stimulate resorption of bone. The clinical significance of this finding is as yet unknown, but as prostaglandins become better characterized, they may assume a more important role in the regulation of bone structure and function.

Increased bone fragility and a radiologic appearance similar to osteoporosis can be observed in a wide variety of hematologic conditions with bone marrow hyperplasia. Carbohydrate and lipid storage diseases may also be associated with bony rarefaction. These disorders are not true osteoporosis, as they are not primary disorders of bone, and differential diagnosis seldom presents a problem. Homocystinuria has also been reported to be associated with osteoporosis.

Recently, cigarette smoking has also been reported to be associated with an increased incidence of osteoporosis. A group of women who smoked one pack of cigarettes or more daily had twice the incidence of vertebral fractures and a higher incidence of significant osteoporosis of the metacarpal bones by x-ray examination. Many of the smokers also had significant chronic pulmonary disease, but the mechanism responsible for the osteoporosis is unknown.[7]

Parathormone levels have been measured in patients with advanced osteoporosis and found to be elevated.[3] This finding has several possible interpretations: the parathyroid hyperactivity might be primary, it might be secondary to dietary factors or early renal disease, or it might be a consequence of established osteoporosis. The incidence of osteoporosis in patients with hypoparathyroidism is lower than average, but it has been argued that this may be a result either of the hormonal changes or of long-term calcium supplements given as therapy. Further studies are needed to clarify these findings.

The majority of patients with osteoporosis are found to have none of the above conditions, with the exception of estrogen lack in the case of women. Because of this, a number of theories have been advanced to account for the "common or garden variety" of osteoporosis. One commonly accepted theory is that osteoporosis is a normal feature of aging, comparable to graying of the hair or decreasing carbohydrate tolerance, and should not be considered as a disease at all. Serial measurements of bone density show that bone density is greatest in early adult life, and that from the third decade on there is a progressive bone loss with age. Nevertheless, there is wide variation in the amount of bone lost with age, and when painful or even life-threatening fractures result, it is difficult to regard the state as normal. What is needed is a guide to differentiate physiologic from pathologic bone loss.

PREVENTION OF OSTEOPOROSIS

Much controversy has surrounded the prevention and treatment of osteoporosis partly because the nature of the disease is obscure. Attempts have been made to prevent the development of osteoporosis with long-term estrogen treatment. Several groups have reported limited success in preventing fractures, and bone loss proceeded at a slower rate.[8,11] Bone loss occurred even with estrogen treatment, however, and one group noted the development of an unexpectedly high number of endometrial carcinomas. This adverse effect of estrogens has recently been confirmed by other workers. The use of estrogens for the prevention of osteoporosis, therefore, should be considered only in women who have had a total hysterectomy. The common practice of removing normal premenopausal ovaries at the time of hysterectomy should be condemned, since many more women die as a consequence of fractures than as a result of ovarian cancer.

No long-term prospective studies have been done on the role of diet in osteoporosis. However, an adequate calcium intake—800 to 1000 mg daily—should be maintained. Skim milk contains as much calcium as whole milk and is preferred for those patients who should restrict their intake of calories or animal fats. Two glasses of milk, a reen leafy vegetable, and two or three slices of bread daily would barely supply these needs. Patients intolerant of dairy products should be given calcium tablets.

Because osteomalacia and osteoporosis may coexist, an adequate intake of vitamin D is also necessary. Vitamin D is added to all commercially available milk. Patients who do not drink milk should receive vitamin D supplements.

High protein diets are contraindicated in both the prevention and the treatment of osteoporosis. Short-term studies in osteoporosis patients have demonstrated that protein supplements cause increased calcium losses. A diet containing no more than 7 ounces daily of fish, meats, or eggs should be prescribed. Such a diet is also felt to be indicated in the prevention of coronary disease.

Although it seems obvious, the various known causes of osteoporosis must be avoided if osteoporosis is to be prevented. Adrenal steroids should be used sparingly and for as short a time as possible. Patients should be kept ambulatory, or rehabilitated as soon as possible following neurologic or orthopedic problems. Conditions such as hyperthyroidism or hyperparathyroidism should be diagnosed and treated promptly.

TREATMENT

The treatment of established osteoporosis has been frustrating because none of the proposed treatments has ever been shown to result in an increase in bone density. Estrogens have been shown to have a positive effect on short-term calcium balance, but no long-term effects. Administration of calcium, with and without vitamin D to promote absorption, has also failed to cause demonstrable calcium retention for more than a short period of time. A variety of androgens and anabolic agents have also been used, because their effect on nitrogen balance was expected to promote new bone formation, but this claim has not been borne out.

Several new agents have recently been proposed for the therapy of osteoporosis. Calcitonin, which is secreted by the parafollicular cells of the thyroid and directly inhibits bone resorption by inhibiting osteoclastic activity,[14] has been available for human use recently. Although it has been very helpful in the treatment of Paget's disease, it has not been useful in the treatment of osteoporosis because the decrease in bone resorption is accompanied by an equal or greater decrease in bone formation.

A low incidence of osteoporosis has been reported in residents of North Dakota where the fluoride content of the drinking water was 4.0 to 5.8 ppm.[4] Attempts to treat osteoporosis with high, medium, and low doses of fluoride have been made; the crystal structure of newly formed bone is altered when high doses of fluoride are given, but the strength and density of the bone are not increased. It appears that for fluoride to have a protective effect against osteoporosis, it must be given for long periods of time.

A third new approach recently tried in osteoporosis is the use of compounds called diphosphonates. These compounds were derived as analogues to pyrophosphate, and are two-carbon compounds with two phosphate groups attached to one of the carbon atoms. They inhibit the dissolution of hydroxyapatite in vitro, but in vivo experiments have been disappointing and at present these compounds are not considered to have any clinical use.

Pain is a frequent problem in osteoporosis and its treatment is essential, not only for humanitarian reasons, but also because pain leads to immobilization which will accelerate the osteoporotic process. Because of the chronicity of the problem, opiates should not be used. Muscle relaxants may be helpful if muscle spasm is present; the theoretical disadvantages of decreasing muscular tension on bone are outweighed by the advantages of mobilizing the patient.

Prevention of fractures is an important part of the therapy of osteoporosis, and a part which is frequently neglected. Accidents are one of the leading causes of death in the elderly, and the majority of fatal accidents are associated with fractures.[12] The two most hazardous areas for older patients are the streets and the bathroom. Patients who are unsteady on their feet should be provided with a cane and instructed never to leave the house without it. Patients with osteoporosis should never walk in snow or on ice. Bath tubs should be provided with railings or other solid support for grasping. All loose rugs should be removed, and the free edges of larger carpets nailed to the floor. Vertebral fractures occur during lifting, often a grandchild or a window sash. Heavy lifting should be cautioned against. Despite all these precautions, osteoporosis may be complicated by fractures, often after only minor trauma.

Although patients with symptomatic osteoporosis are difficult to treat, the overall course of osteoporosis is often characterized by long periods of freedom from pain and fractures.[2] This is particularly true with regard to vertebral fractures, and once dorsal kyphosis advances to the stage where the ribs come to rest on the pelvic brim, further fractures seldom occur and back pain becomes less severe. Patients may continue to be active and relatively free of pain even after several episodes of painful fractures and with severe vertebral deformity. Elderly osteoporotic patients should, therefore, be managed with the goal of returning them to activity. Such an optimistic outlook is good therapy for a patient in pain, and may make the difference between his becoming an invalid and his recovering.

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Endocrinology and Metabolism Division
Coney Island Hospital
2601 Ocean Parkway
Brooklyn, New York 11235

Host Factors and Infectious Diseases in the Elderly

Jules L. Gladstone, M.D., and Rose Recco, M.D.***

Elderly people differ from young people in their susceptibility and response to certain infectious agents. These differences vary depending on the identity of the specific organism which invades the host. For example, the viral exanthematous diseases are much less frequent in the elderly, notwithstanding the increased incidence of herpes zoster or shingles in this age group. Furthermore, the incidence of influenza virus, meningococcal and Haemophilus influenzae infections is much higher in children and/or young adults. The reasons for this are complex, but may include prior experience of the older individual with these agents at an earlier age and less exposure to groups of people, particularly to school children. On the other hand, gram-negative bacteremia is much more common in an elderly hospital population than in a young one, and deaths from bronchopneumonia during an influenza epidemic are found predominantly in the age group over 60. The authors will discuss some of the host factors that are altered in the elderly which contribute to this changing pattern of resistance to infection.

Physicians taking care of older patients should be aware of changes in the clinical presentation of many major infections such as infectious endocarditis, meningitis, urinary tract infection, and bacteremia. Later in this review we shall discuss these entities in greater detail. In addition, we shall deal with vascular and decubitus ulcers, which frequently cause serious infections in elderly people. Finally, we shall briefly review antibiotic therapy with advice on pitfalls to avoid in the elderly.

HOST FACTORS

Studies by Price and Makinodan of young and old mice revealed an actual increase in the thymus-derived (T) cells and a decrease in bone-marrow (B) derived lymphocytes in the spleens of aged mice.[30] Both T and B cells of old mice were less capable of growth and proliferation than the respective young cell populations. Other experiments indicated that noncellular factors, presumably at a chemical level in the old mice, had a detrimental effect on antibody forming cells.[31] Quantitative analysis revealed that the senescence of the lymphocyte, rather than humoral factors, was the major determinant of decreasing immunologic function in the aging mouse.

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*Chief, Division of Infectious Disease, Coney Island Hospital; Assistant Professor of Medicine, State University of New York, Downstate Medical Center, Brooklyn

**Physician-in-Charge of Antibiotic Surveillance Program, Coney Island Hospital; Instructor in Medicine, State University of New York, Downstate Medical Center, Brooklyn

Studies in man have found a similar trend toward decreasing immunologic reactivity in the aged. Weksler and Hutteroth demonstrated that lymphocytes from elderly people have a decreased mitogenic response to plant mitogens and allogeneic lymphocytes.[45] This decreased mitogenic activity was attributed to a malfunction of T cells. Cell-mediated immune function was further tested by Roberts-Thomson et al., using three systems: delayed type hypersensitivity skin tests, lymphocyte response to phytohemagglutinin, and T-cell dependent IgG response to monomeric flagellin.[32] Young people (under 25) showed significantly greater responsiveness than the older group (over 60). Moreover, these investigators showed that the mortality rate of the people over 80 years of age who were hyporesponsive in tests of delayed hypersensitivity was significantly greater over a two year period than that of a comparable group who were immunologically more responsive.

Buckley and Dorsey studied serum immunoglobulin levels of 811 healthy people aged from birth to 92 years by means of a quantitative single radial diffusion method.[8] Maximum immunoglobulin levels were reached in the third decade. Average IgM levels decreased significantly by the sixth decade, and IgG decreased significantly from the third through the sixth decade. Changes in IgA levels after maturity were not significant. Longitudinal studies performed at the same center revealed that in a group of 143 apparently healthy individuals over age 40, levels of IgG and IgA increased in two thirds of the subjects over a period of almost 2 years of observation.[7] The point of the observations is that immunoglobulin levels tended to decline with aging, but the subset of survivors had higher levels of immunoglobulin than the group who died. One can only conjecture whether higher concentrations of circulating immunoglobulins and/or greater levels of cell mediated immune responsiveness actually promoted longevity.

A highly significant study performed by Howells et al.[20] compared the response of a group of 440 residents of old peoples' homes to a multivalent influenza virus vaccine with that of a group of young adults living in the same community. The older people developed a lower level of antibody to both A2 and B components than the younger group. Nevertheless, the vaccinated group showed a significantly lower incidence of bronchopneumonia and overall mortality than the unprotected age-matched group.

In addition to the decline in resistance to infection which can be detected in a healthy, aging population, many other changes in resistance result from disease states which are more frequent in older people. For example, polymorphonuclear phagocytes from patients with diabetes mellitus[26] and myeloproliferative disorders[28] show impaired migration in response to chemotactic stimuli. Also, the hyperosmotic environment of the diabetic has been shown to be inimical to neutrophilic ingestion.[12] Chronic lymphatic leukemia and multiple myeloma are examples of lymphoproliferative diseases associated with defective production of immunoglobulin in response to antigenic stimuli. Patients with established, severe bacterial infections are particularly at risk because their granulocytes have an acquired reduction in bactericidal efficiency.[28] This deficit is found in those patients with toxic granulations in their neutrophils and is resolved when the infection subsides.

Some chemotherapeutic agents used to treat malignancies, collagen vascular diseases, or to prevent transplant rejection can adversely affect the normal defense mechanism. Cytotoxic immunosuppressive drugs and radiation therapy may directly destroy the myeloid-producing cells of the bone marrow, resulting in severe granulocytopenia. Corticosteroids can impair leukocyte migration,[6] and corticotropin can reduce the manifestations of delayed hypersensitivity.[35] In addition, protein calorie malnutrition, a likely accompaniment of many diseases that afflict the aging, has recently been shown to cause a deficiency of the proactivator of the third component of complement in children.[37]

The aging are prone to develop obliterative disease of the circulatory system, particularly if they have diabetes. This may result in infarctions of the skin of the lower extremities, which permits colonization and invasion by bacteria. Cerebrovascular disease often results in a reduced level of consciousness, thereby increasing the likelihood of aspiration pneumonia and decubitus ulcers. The frequent occurrence of femoral fractures in this age group, necessitating operative intervention has similar consequences.

The rising incidence of prostatic hypertrophy and carcinoma in aging men is accompanied by an increased frequency of urinary tract infection and gram-negative bacteremia. Diagnostic and operative manipulations and the use of indwelling bladder catheters provide a portal of entry for bacterial invaders. The increased frequency of asymptomatic bacteriuria in the elderly of both sexes is indicative of a breakdown of local resistance against bacterial colonization of the urinary tract in the presence of sustained defense against dissemination.

INFECTIOUS ENDOCARDITIS

The occurrence of endocarditis in patients over the age of 60 years can no longer be considered rare. With a longer life expectancy and the use of antibiotics, not only has the average age of the patient with bacterial endocarditis increased, but the percentage of cases over the age of 60 has been rising steadily (Table 1). In one major series,[24] 30 per cent of these patients were at least 60 years of age, and the average age was 49.7 years. In 1923 only 1.2 percent were 60 years of age and older.

The clinical manifestations of endocarditis in the elderly mimic those in younger patients but are generally less pronounced.[2,11] Fever may be attributed to other commonly occurring infectious conditions, murmurs regarded as "innocent" murmurs and cerebrovascular accidents attributed to arteriosclerosis. If the physician looks carefully, he will find all the features of the disease as it is seen in younger patients. As in younger age groups, males consistently predominate over females, but to a varying degree from 8:1 to 2:1, depending upon the series. There are some features which appear to occur more commonly in older age groups. Anderson[2] found that the disease may have a more insidious onset in the elderly and that embolic phenomena other than petechiae are less common.

Wallach et al.,[43] in an autopsy series which consisted of patients studied predominantly during the antibiotic era, found that endocarditis was more often acute in the elderly irrespective of whether the patient had rheumatic heart disease. In their series, rheumatic valvular disease was present in only about 43 per cent of elderly patients. Carefully performed pathologic studies showed that sclerotic changes in the valves were the most common lesions in the elderly as compared to underlying rheumatic or congenital heart disease in younger patients. Younger patients often had dental manipulation or abortion as the antecedent event, whereas older subjects were more likely to develop the disease following major surgery. Elderly patients more commonly had associated diseases such as urinary tract infection, bronchopneumonia, malnutrition, or

Table 1. *Incidence of Endocarditis in the Elderly*

	AUTHOR	TOTAL CASES	PER CENT OF PATIENTS OVER AGE 60
1923	Blumer, G.[5]	317	1.2%
1940	Hedley, O. F.[19]	118	2%
1948	Clawson, B. J.[9]	417	11.3%
1951	Correll, H. L.[10]	70	10%
1955	Anderson, H. J.[2]	76	18.4%
1955	Afremow, M. L.[1]	202	35%
1961	Friedberg, C. K.[14]	95	19%
1962	Robinson, M. J.[33]	91	30%
1966	Lerner, P. I.[24]	100	30%
1973	Tan, J. S.[40]*	91	22%

*Streptococcus viridans endocarditis only.

diabetes. Virulent bacteria with acute ulcerative lesions were more commonly present in the older group. Younger patients more commonly had rheumatic heart disease with Streptococcus viridans as the most common organism causing the valve lesion of the classical subacute type. Finally, glomerular lesions, both diffuse and focal glomerulonephritis, in their acute and chronic forms, were less common in the elderly. The latter might be explained by the fact that there is a depression of immunologic reactivity in the elderly.

In a more recent series by Thell et al.[41] in 1975, 42 cases of endocarditis in patients over the age of 60 were reviewed. This series reported many of the same observations of previously mentioned series.[2,11] Fever was present in 93 per cent of the cases and murmurs in 68 per cent, yet the diagnosis of endocarditis was made in only 16 cases (40 per cent). This high rate of diagnostic error may be due to the physicians' lack of awareness of the importance of infective endocarditis as a cause of disease in the elderly. Pathologic data were also similar to that of Wallach's series.[43] In Thell's series[41] the most common underlying diseases were calcified or otherwise deformed aortic valves (referred to as arteriosclerotic valves in the earlier literature) and rheumatic fibrosis of the mitral valve. Virulent organisms, particularly Staphylococcus aureus, were most common. These were followed by various types of streptococci, particularly alpha streptococci. Only 2 of 42 cases were caused by enterococci.

No description of endocarditis in the elderly would be complete without some discussion of enterococcal endocarditis. Although the incidence of enterococcal endocarditis has been increasing, it represents only about 10 per cent of the cases of endocarditis in most published series. About 40 per cent of patients are young women in their childbearing years, and 60 per cent are older men. Genitourinary antecedents are common to both groups. In Weinstein's series[24] only 8 of 100 cases were due to enterococci even though 30 per cent were older than 60 and the majority were male. Although enterococcal endocarditis is not the most common form in the elderly, the large number of genitourinary procedures performed in this age group make it an important consideration when prolonged fever follows urinary tract manipulation or infection.

Antibiotic choices in endocarditis do not differ from those prescribed for younger patients and are tabulated in Table 2. If endocarditis is recognized and properly treated, the morbidity and mortality do not differ significantly from that in younger patients,[4,11,24,40]

In summary, it is important to remember that the sclerotic valve, especially if its surface becomes distorted by the deposition of calcium in its leaflets or its function impaired by a damaged papillary muscle, can serve as a nidus for infection. Virulent organisms, especially Staphylococcus aureus, are the most common. Furthermore, since endocarditis frequently follows operative procedures, preoperative prophylactic antibiotic therapy in patients with sclerotic valves or papillary muscle dysfunction may be as important to the older patient as it is to younger patients with rheumatic or congenital heart disease.

MENINGITIS

Meningitis in patients over the age of 60 is most commonly caused by Diplococcus pneumoniae. Viral, fungal, and other forms of bacterial meningitis such as Haemophilus influenzae meningitis do occur in the elderly but are not common and will not be considered here. Because the number of diseases that resemble meningitis is increased in this age group, physicians may miss the diagnosis of meningitis because of failure to think of it. The signs and symptoms of this disease (fever, headache, lethargy or confusion, vomiting, irritability, and stiff neck) are present in the majority of patients and do not differ appreciably from younger patients with pneumococcal meningitis. Predisposing factors such as upper respiratory infections, otitis media, pneumonia and head trauma occur with about the same frequency in both young and old patients with this disease.

The diagnosis is made in the usual manner, and initial treatment is based on cerebrospinal fluid findings and gram stain. If the gram stain is negative or inconclusive, a counter immunoelectrophoresis can be performed to help clarify the diagnosis, pending receipt of culture. Our choices of antibiotics for bacterial meningitis are listed in Table 3. Therapy is continued in high dosage parenterally until the patient has been afebrile for 5 days; his cerebrospinal fluid shows less than 30 cells per mm^3, none of which are polymorphonuclear leukocytes; and chemical parameters of the cerebrospinal fluid are improving.

Mortality rates vary from 10 to 65 per cent, depending upon the series, but the highest mortality rate is in patients over the age of 60. In addition to age, other factors such as delay in starting therapy, coma, bacteremia, and coexisting illness contribute to increased mortality. Weiss et al.[44] analyzed all the factors contributing to a poor prognosis in pneumococcal meningitis. In his study, coexisting illness was found to be the most important factor. Most patients who die of pneumococcal meningitis have a potentially fatal illness such as nonpneumococcal

Table 2. *Antibiotic Therapy of Bacterial Endocarditis in the Aged*

ORGANISM	REGIMEN OF CHOICE	ALTERNATE REGIMEN
Streptococcus viridans	Penicillin G, 6 to 20 million units daily I. V. for 4 weeks *or* Penicillin G, with streptomycin, 0.5 gm. I.M. q 12h, both for 3 weeks.	Cephalothin or vancomycin
Enterococcus	Penicillin G, 20 million units, or ampicillin, 12 gm. daily I.V. combined with streptomycin, 0.5 gm I.M. q 12 h (Kanamycin or gentamicin may be used instead of streptomycin) for 4 to 6 weeks.	Vancomycin with streptomycin
Staphylococcus aureus		
Penicillin-sensitive	Penicillin G, 20 million units daily I.V. 4 to 6 weeks	Cephalothin or vancomycin
Penicillin-resistant	Oxacillin or methicillin or nafcillin, 12 gm daily I.V. 4 to 6 weeks.	
Staphylococcus epidermidis		
Penicillin-sensitive	Penicillin G, 20 million units I.V. daily for 4 to 6 weeks	Variable, but a cephalosporin or vancomycin may be effective
Penicillin-resistant	Oxacillin or methicillin or nafcillin, 12 gm daily I.V. for 4 to 6 weeks.	
Unknown organism (culture negative or pending)	Penicillin G, 20 million units I.V., and oxacillin, 12 gm I.V., and an aminoglycoside parenterally daily for 4 to 6 weeks.	Vancomycin with streptomycin

Table 3. *Antibiotic Therapy for Bacterial Meningitis in the Elderly*

ORGANISM	REGIMEN OF CHOICE	ALTERNATE REGIMEN
Pneumococcous	Penicillin G, 2 million units I.V. q 2 h daily for approximately 14 days	Chloramphenicol
Meningococcous	Penicillin G, 2 million units I.V. q 2 h for approximately 10 days	Chloramphenicol
Staphylococcus aureus		
Penicillin-sensitive	Penicillin G, 2 million units I.V. q 2 h daily for approximately 4 weeks	Densensitize and treat with penicillin G I.V.; *or* cephalothin I.V. with intrathecal cephaloridine
Penicillin-resistant	Methicillin, 1 gm I.V. q 2 h for approximately 4 weeks.	Desensitize and treat with methicillin I.V.; or cephalothin I.V. with intrathecal cephaloridine
Unknown organism	Penicillin G, 2 million units I.V. q 2 h daily, or ampicillin, 2 gm I.V. q 4 h daily for variable time depending on response	Chloramphenicol

pneumonia, cardiac or renal disease, or sickle cell disease, in addition to meningitis. The fatality rate was more than four times as high among patients with associated disease than those with none, irrespective of age. However, the number of associated diseases markedly increases with age, hence the increased mortality in the elderly. Coma and bacteremia reflect collapse of local and systemic resistance to bacterial invasion and signal a poor prognosis in any age group.

URINARY TRACT INFECTION

The prevalence of significant bacteriuria rises steadily throughout life. It is much higher in females early in life. During middle age and beyond, the rate rises rapidly in males to the point where it approaches that of females. Our study of 100 people, median age 70, confined to an extended care facility, revealed an overall prevalence of 19 per cent, which is consistent with the findings of other investigators who have examined institutionalized geriatric populations.[16] The rate for women (27 per cent) was higher than that for men (17 per cent). However, this difference is not significant in these small groups.

For the practicing physician, a most important question is how to approach the problem of asymptomatic bacteriuria, which affects such large numbers of apparently healthy older people. Fortunately, we now have certain information that enables us to concentrate our efforts on the so-called high risk group. Stamey has pointed out that there are 3 groups of people who are at risk of developing chronic pyelonephritis with scarring of the kidney and progressive renal failure: children with bacteriuria associated with vesicoureteral reflux, individuals with mechanical obstruction to urine flow, and those with neurogenic bladders.[39] This concept received support from the study of Kimmelstiel who found only an 0.1 percent rate of nonobstructive chronic pyelonephritis in 3393 autopsied cases.[22] Schechter et al. studied the etiologic diagnoses of 173 patients with chronic renal failure at a dialysis center in an attempt to define the role of urinary tract infection.[36] Twenty-two patients were diagnosed as having chronic pyelonephritis based on chemical and cultural criteria, all of whom had obvious structural lesions such as calculi, congenital obstruction, hypoplasia, or bilateral reflux. Nineteen of these 22 patients with chronic obstructive pyelonephritis had either symptomatic urinary tract infection or attempted surgical correction prior to the onset of azotemia. The data support the conclusion that the efforts of physicians to prevent chronic renal insufficiency should be directed at those patients with urinary tract infection who have symptoms of sepsis or obstructive uropathy which cause them to seek medical care, rather than at those with asymptomatic bacteriuria.

The syndrome of dysuria, frequency, rigors, fever and pain in the flank or suprapubic region is strongly indicative of urinary tract infection. Elderly patients and those with indwelling bladder catheters may have fever and chills with no localizing symptoms. Patients with chronic pyelonephritis usually do not manifest the classic symptoms of sepsis; they may be completely asymptomatic until chronic renal failure develops, bringing with it the syndrome of urinary frequency, lassitude, anorexia, and pruritus. This syndrome is not specific for infectious renal disease.

The urinalysis will usually show mild to moderate proteinuria, with significant pyuria (5 or more white blood cells) and occasionally white blood cell casts indicative of renal tubular inflammation. The most significant laboratory test is the quantitative culture and colony count, using pour plates or quantitative loops. The specimen should be collected in the morning, prior to drinking fluids, or starting treatment, after careful cleansing of the urethral orifice so as to avoid contamination by surface bacteria. Elderly patients will require careful instruction regarding the cleansing of the external urethral orifice, and the initial 5 to 10 ml of urine should be discarded before collecting a mid-stream urine specimen. If a patient with suspected urinary sepsis is unable to cooperate, it may be necessary to collect a sterile urine specimen by catheterization, but this technique causes infection in approximately 2 to 6 per cent of patients and should be used with discretion. The most accurate method of obtaining urine is the suprapubic puncture. Unfortunately, it is unpleasant for the patient, and is therefore rarely used. The criterion for significant bacteriuria is 100,000 colonies per ml of properly collected and promptly processed urine. This figure does not apply to urine collected by bladder catheterization, where a count of 10^3 is indicative of infection, nor to urine obtained by suprapubic puncture where any quantity found is considered abnormal.

There is general agreement that bacterial involvement of the kidney is more likely to cause serious sepsis and deterioration of function than bladder infection. Up to now, the only ways to determine the site of invasion were by retrograde ureteral and bladder catheterization or by a laborious bladder washout technique. New studies by Thomas et al.[42] and Jones et al.[21] have shown that patients whose bacteria are coated with human globulin are likely to have kidney infection. These investigators found a positive correlation between fluorescent antibody staining of bacteria in the urine with renal involvement as detected by clinical or bladder washout methods. With this convenient method, it is possible to detect those patients who have upper tract diseases; they should be treated intensively and have careful follow-up to insure sterility of their urinary tract.

Any patients who develop acute symptomatic urinary tract infection, irrespective of the anatomic state of their urinary tract, should receive prompt antimicrobial therapy. Those with urinary stasis caused by neurogenic bladder, prostatic hypertrophy, calculi, tumor, or stricture should be evaluated for possible surgery by a competent urologist. The organism most commonly responsible for acute urinary tract infection is E. coli, which is usually sensitive to a variety of chemotherapeutic agents. Recurrent and hospital-acquired infections are usually caused by more resistant Enterobacter, Klebsiella, Proteus, Pseudomonas, E. coli, Enterococcus and Staphylococcus organisms. The antimicrobial therapy for infections caused by these organisms is listed in Table 4.

Follow-up cultures should be done at 2 and 6 weeks and at 6 months. If a relapse with the same organism that caused the original infection is detected, the patient is presumed to have renal involvement and should receive a 6 week course of a potent chemotherapeutic agent. Unfortunately, the availability of serotyping of E. coli is very limited; one may have to use other methods such as the detection of human globulin-coated bacteria, to aid in deciding which patients require prolonged therapy.

Those individuals who suffer from symptomatic reinfections, that is, recurrences with altogether new bacterial pathogens, are likely to have lower tract disease and are not likely to benefit from prolonged intensive therapy. Each episode should be treated for 10 to 14 days; if reinfections are frequent, it may be useful to initiate a long-term chemoprophylactic regimen, employing methenamine hippurate or mandelate with acidification, nitrofurantoin, a sulfonamide, or trimethoprim-sulfamethoxazole. The latter agent is particularly useful in male patients with recurrent urinary tract infection associated with chronic prostatitis: it is the only drug which has been shown to achieve a therapeutic concentration in the prostate. Patients with asymptomatic bacteriuria, who have none of the high risk factors mentioned previously, should receive a

Table 4. *Antibiotic Therapy for Urinary Tract Infection in the Elderly*

ORGANISM	ORAL AGENT	PARENTERAL AGENT
Escherichia coli	Ampicillin, or a cephalosporin or a sulfonamide	Gentamicin or tobramycin or kanamycin
Klebsiella pneumoniae	A cephalosporin or tetracycline or trimethoprim-sulfamethoxazole	Gentamicin or tobramycin or kanamycin
Enterobacter	Trimethoprim-sulfamethoxazole or tetracycline or nalidixic acid	Gentamicin or tobramycin or kanamycin
Proteus mirabilis	Ampicillin or a cephalosporin or trimethoprim-sulfamethoxazole	Gentamicin or tobramycin or kanamycin
Other proteus	Trimethoprim-sulfamethoxazole or oral carbenicillin or nalidixic acid	Gentamicin or tobramycin or carbenicillin
Pseudomonas aeruginosa	Oral carbenicillin	Gentamicin or tobramycin with parenteral carbenicillin; or a polymyxin
Enterococcus	Ampicillin or Amoxicillin or nitrofurantoin	Ampicillin or vancomycin
Staphylococcus aureus		
Penicillin-sensitive	Penicillin V or a cephalosporin	Penicillin G or a cephalosporin
Penicillin-resistant	Dicloxacillin or a cephalosporin	Oxacillin or a cephalosporin

course of therapy for 10 to 14 days with a nontoxic yet effective agent, if such an agent is available. Since the morbidity and mortality of people with this syndrome are usually little influenced by bacteriuria, it is unwise to treat these individuals aggressively with toxic drugs.

The elderly suffer a high risk of urinary tract infection and septicemia from operations on the urinary tract and during prolonged bladder catheterization. On the basis of several studies of postoperative infection rates in urologic surgery, it is clear that urosepsis is much less frequent in patients who are bacteriuria-free at the time of surgery. Therefore, every effort should be made to treat infections of the urinary tract preoperatively, so as to eliminate this adverse factor. The use of chemoprophylaxis in patients without bacteriuria who undergo urological surgery to further reduce infection rates is still controversial. Plorde et al.,[29] employing parenteral kanamycin, and Wilson et al.,[46] using parenteral cephalothin starting a few hours before surgery and continuing during the period of postoperative catheterization, were successful in reducing the incidence of urosepsis in the bacteriuria-free groups. Furthermore, Wilson found that the postoperative use of the three-way Foley catheter with continuous antibiotic rinse (neomycin-polymyxin B) was also effective under the same conditions. Further studies of each of these regimens should be carried out in order to confirm their efficacy in the prophylaxis of urinary tract sepsis following urologic surgery.

The high incidence of urosepsis resulting from indwelling bladder catheterization is well known. Studies of the closed sterile drainage system, using the conventional two-way catheter[23] or the three-way catheter with antibiotic drip[17] have shown that both methods are effective in delaying the onset of infection in those patients who are free of bacteriuria at the onset of catheterization. The rigid application of either technique combined with frequent bacteriologic monitoring of the urinary bacterial flora may help to reduce the high incidence of urosepsis and gram-negative bacteremia in hospital practice.

BACTEREMIA IN THE ELDERLY

The mortality rates of bacteremia caused by facultative gram-negative bacilli, bacteroides species, pneumococcus, and staphylococcus rise progressively with increasing age over 40. It is vital that the diagnosis of sepsis be made promptly so that appropriate antibiotic therapy may be initiated. The classic syndrome consists of chills, fever, prostration, and occasionally nausea and vomiting, but unfortunately the elderly patient may merely manifest confusion, stupor, delirium, or agitation.[25] Fever may be minimal or absent in the elderly. Hypothermia is rarely found. The sudden development of hypotension, oliguria, thrombocytopenia, tachypnea, or acidosis without apparent cause should prompt an immediate search for infection. The arterial blood gas analysis may show a respiratory alkalosis which progresses to a mixed respiratory alkalosis–metabolic acidosis if the septicemic state continues. The clinical setting of the patient may provide clues to the underlying cause, for example the presence of a urinary or vascular catheter, tracheal intubation with an intermittent positive pressure respirator, or granulocytopenia. Occasionally one may see vesicular skin lesions filled with cloudy fluid surrounded by erythematous margins which progress to ulceration, characteristic of pseudomonas septicemia (echthyma gangrenosum). If a patient suddenly manifests any of these signs and/or symptoms, the physician should immediately obtain blood cultures, cultures of suspicious local sites, and gram stain of body fluids at these foci.

If the evaluation of evidence from clinical and laboratory sources indicates the possibility or probability of bacteremia, the physician should institute antimicrobial therapy promptly. The decision as to which agent or agents to use is determined by probable site of origin of infection. One next decides which bacterial species is most likely at this location and then selects the most effective and least toxic chemotherapeutic agent for use against this organism.

CHRONIC SKIN ULCERS

The elderly are particularly susceptible to ulcerations of the lower extremities caused by arterial or venous obstructive disease. Although the primary etiology is ischemia or stasis of circulation, bacteria usually colonize or invade tissue which is devoid of the protection provided by the epidermal layers of the skin. Our study of the bacterial flora of arterial and venous ulcers showed a much higher colony count in these lesions than in the surrounding unbroken skin.[15] Clinically inflamed ulcers were generally invaded by virulent bacteria such as Staphylococcus aureus or members of the Enterobacteriaceae, whereas the bland ulcers were usually colonized by bacteria of lower virulence such as Staphylococcus epidermidis. The use of systematic antibiotics to treat invasive infections originating in vascular ulcers is essential if one is to preserve the viability of the involved extremities. The choice of antibiotic should be based on the sensitivities of the offending bacteria. Because blood flow to the infected tissue is inadequate, it is necessary to utilize maximal parenteral dosages in an effort to achieve therapeutic levels where they are most needed.

Another skin lesion that may be the focus of serious local sepsis or bacteremia is the decubitus ulcer. This erosion of normal skin occurs frequently in aged patients who are confined to bed because of cerebral infarcts, senile dementia, disorders of basal ganglia, or fractures of bones of the lower extremities. The underlying cause in each of these diagnostic categories is unremitting pressure transmitted to skin, subcutaneous tissue, and muscle over bony prominences. Arterioles and capillaries are compressed, resulting in ischemia and subsequent necrosis which rapidly involve all tissue between skin and bone. By the time one sees erythema on the overlying skin, the underlying subcutaneous tissue and muscle may already be severely damaged. The use of sedatives which produce immobility and the practice of maintaining the supine patient with the head of the bed elevated both increase the likelihood of decubitus ulceration.[13] Fecal and urinary contamination of decubiti is likely to add to the risk of infection. The usual flora of decubiti is composed of gram positive cocci, either Staphylococcus aureus or Enterococcus, combined with gram negative bacilli, consisting of one or more species of Enterobacteriaceae and/or Pseudomonas aeruginosa. Ulcers containing necrotic tissue soiled by feces may harbor anaerobic organisms such as Clostridrum or Bacteroides species.

In order to prevent the development of these lesions, the physician should identify the patients at risk and order them turned every two hours, day and night. Correction of dehydration and maintenance of a positive nitrogen balance are important factors in sustaining normal skin turgor. Heel pads and a well padded foot board are helpful in reducing the shearing forces which operate in the semirecumbent position. If a pressure sore develops despite prophylactic measures, local debridement of necrotic tissue, followed by gentle cleansing and application of nontoxic and nonsensitizing antiseptic ointments or solutions should be ordered. Preliminary clinical trials employing ointments containing proteolytic enzymes to debride ulcers have met with some success. These preparations deserve further, controlled studies. Alternating pressure mattresses, Stryker frame, and various types of mattresses containing air, water, and polyurethane foam have each been credited with therapeutic value by some clinicians, but require more critical trials to assess their efficacy. If the ulceration shows evidence of local inflammation with warmth, purulent exudate and redness of surrounding intact skin, and especially if fever, leukocytosis or bony involvement is also present, the physician should collect specimens for aerobic and anaerobic cultures of the ulcer and blood and start treatment with appropriate systemic antimicrobial therapy. The patient should be positioned so as to avoid pressure over the ulcer and must be turned frequently to avoid new areas of breakdown.

ANTIMICROBIAL THERAPY

The recommendations for the treatment of some of the more commonly encountered bacterial infections in elderly patients are listed in Tables 2, 3, and 4. A detailed description of the pharmacology of the antimicrobial agents listed in these tables is beyond the scope of this article.

The antibiotic regimens for infective endocarditis and meningitis (Tables 2 and 3) must all be administered parenterally. All organisms from the blood or spinal fluid should be tested for antimicrobial sensitivity in the laboratory to verify their susceptibility to the agents used. If the patient is allergic to penicillin, he must be presumed to be sensitive to all penicillin-derivatives. The use of an alternate agent or desensitization prior to treatment with a penicillin-type drug is recommended.

In treating urinary tract infections, the physician must not only select the most appropriate agent, but must also decide on the route of administration. The regimens are divided into an oral one for lower urinary tract infections without systemic involvement and a parenteral one for upper tract or renal infection with possible bacteremia. Since the antimicrobial sensitivity patterns of the gram-negative bacilli are variable, the choices of oral agents for these organisms are necessarily multiple and must depend ultimately on laboratory testing. Knowledge of the agents listed is of value in the interval of time between the identification of the organism and the determination of its antibiotic susceptibilities. The choices of antibiotics for parenteral treatment of the systemic infections are more limited, making it possible for the physician to select agents prior to laboratory confirmation. For example, if a patient has acute pyelonephritis with severe systemic symptoms caused by an ascending urinary tract infection of unknown etiology, the use of ampicillin plus gentamicin or tobramycin is likely to be effective in almost all cases.

The choice of antimicrobial agent in the elderly and the changes in dosage based on alterations of renal, hepatic, or cardiovascular function are basically similar to those in younger patients. There are, however, some differences which must be kept in mind. Kidney function declines with advancing age, and those agents which depend almost exclusively on the kidney for excretion are likely to accumulate in the body if given in full dosage for prolonged periods of time. Both kanamycin and gentamicin can cause impairment of renal function. Kanamycin can cause deafness through irreversible cochlear damage, especially in the elderly patient who may have pre-existing renal disease. Gentamicin's most frequent toxic effect is on the vestibular cells, resulting in labyrinthine intoxication. Unfortunately, studies by Barza et al. have shown a rather unpredictable correlation between peak level and serum half-life of gentamicin and dosage based on measurement of body weight and serum creatinine.[3] The use of an accurate and rapid system for monitoring blood level of potentially nephrotoxic antibiotics, such as the microassay method described by Sabbath et al.,[34] can help the physician select doses which would be effective and yet avoid toxic concentrations in the blood.

Another agent whose use must be carefully monitored in the elderly is carbenicillin, which contains 4.7 mEq of sodium per gram. A patient who is treated with 30 grams per day intravenously receives 141 mEq of sodium daily. The elderly patient with limited cardiovascular reserve may readily suffer congestive heart failure under these circumstances. Hypokalemia and a bleeding diathesis have also been reported with this agent.

SUMMARY

Because of declining function of their immunologic and other organ systems, elderly individuals are more susceptible to certain types of infections of their heart valves, meninges, urinary tract, and skin. They may develop serious sepsis with subtle clinical signs and symptoms, which makes accurate diagnosis difficult. The antimicrobial agents of choice for use against the organisms most commonly responsible for these septic syndromes are listed in Tables 2, 3, and 4. Some methods of preventing these infections are discussed, but further studies to verify old techniques and establish new ones are needed.

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Coney Island Hospital
2601 Ocean Parkway
Brooklyn, New York 11235

The Increasing Problem of Malignancy in the Elderly

New Concepts in Diagnosis and Management

*Patrick R. Bergevin, M.D.**

The increased incidence of cancer in the elderly has been variously attributed to (1) prolonged exposure to carcinogens and (2) failure of immunologic surveillance, i.e., dysfunction in the thymus-dependent immune system for recognition and destruction of incipient neoplastic cells. This is exemplified by Monroe's[9] report of a cancer prevalence rate of 12 per cent in persons over 60 years of age, increasing to 24.8 per cent at postmortem examination.

Suen et al.,[11] in a study of 3535 consecutive autopsies of patients over 65 years of age, showed that 1149 patients (32.5 per cent) had one or more cancers. In this elderly population, men were affected by malignancy nearly twice as frequently as women (40.3 versus 23.9 per cent), with cancers of the lung, prostate, and gastrointestinal tract constituting most of the cases. In addition it was shown that with advancing age, there was an increased number of occult neoplasms, the most frequent being cancers of the prostate, kidney, and colon. A total of 324 such occult, or incidental, cancers were found at autopsy in the series, representing 29 per cent of the total number of malignancies. One hundred ten of the 1149 cancer patients (9.6 per cent) had more than one cancer. The authors also pointed out that cancer tended to metastasize less frequently in the elderly.

The elderly patient with a suspected cancer frequently poses diagnostic and therapeutic problems which are unique to his age population. The symptoms and signs of malignancy are often masked by the more frequent debilities of old age, such as degenerative arthritis, vascular disease, and impaired bowel and urinary function. The physician must separate the typical from the atypical in these cases in order to pursue a logical diagnostic study. Weight loss and anorexia, for example, should suggest an underlying malignancy and should not simply be ascribed to old age. Aversion to meat is often part of the anorexia of malignancy.

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*Chief, Oncology Division, Coney Island Hospital; Assistant Professor of Medicine, State University of New York, Downstate Medical Center, Brooklyn

Skeletal pain caused by malignant bony deposits may differ little from the pain of osteoarthritis or compressed vertebrae secondary to diffuse osteoporosis. Roentgenographic studies or bone scanning with radioactive compounds may suggest malignancy, and a bone biopsy or aspirate from the painful bone may reveal malignant cells. Sometimes a standard posterior iliac crest biopsy may reveal malignancy when the process is widespread as in multiple myeloma or certain solid tumors such as breast or bronchogenic carcinoma. Biopsy of an enlarged lymph node may reveal malignancy when no primary site is obvious clinically. In this case, the pathologist should be consulted and the biopsy material reviewed with him. Pertinent clinical data can then be supplied which may allow a realistic differential diagnosis and suggestions for further studies.

Paraneoplastic or ectopic hormone syndromes are also examples of distant effects of tumors which, like weight loss and anorexia, are often corrected by successful treatment of the underlying malignancy. Predominantly "foregut" tumors, such as oat cell carcinoma of the lung, thymoma, and pancreatic adenocarcinoma, may secrete ACTH, leading to clinical evidence of adrenal hyperplasia. These patients frequently present with weakness secondary to profound hypokalemia. There are usually no stigmata of the classical Cushing's syndrome because of the patient's short survival. The inappropriate antidiuretic hormone syndrome is most often related to bronchogenic carcinoma; the patient may present with nausea and vomiting, muscle weakness, convulsions, or coma. Hypercalcemia secondary to metastatic bone disease or parathormone production by the tumor (usually bronchogenic and renal cell carcinoma) is frequently seen. The presentation may be with nocturia, nausea and vomiting, constipation, weakness, somnolence, or even coma. Gonadotropins secreted by a tumor may cause gynecomastia. Hypoglycemia is seen in islet cell tumors of the pancreas, mesothelial tumors, hepatoma, and others. Production of insulin by the tumor may be documented in some cases. Hypoglycemia is occasionally observed as an unusual increase in appetite in the terminal phase of a malignancy.

Typical or atypical carcinoid syndromes may be seen with mid gut and foregut tumors respectively. The typical carcinoid syndrome is well known. In atypical carcinoid, there are fewer of the well known signs and symptoms. The facial flush is often a vivid red with facial swelling, lacrimation, and increased salivation lasting several days.

In carcinoma of the lung, digital clubbing is not uncommon and may be associated with painful joints and edema of the extremities (hypertrophic pulmonary osteoarthropathy). There is thickening of the periosteum of the long bones which may be painful. The painful joints are rheumatoid-like but usually spare the hands.

Skin lesions may be an early manifestation of an internal malignancy. Acanthosis nigricans consists of dark, velvety lesions in body folds and is often associated with intra-abdominal carcinomas, especially gastric. Bowen's disease is a psoriasis-like condition which is actually an intra-epithelial squamous cell carcinoma and may be associated with an internal cancer.

Polymyositis, dermatomyositis, myasthenia, peripheral neuropathy and radiculopathy, myelopathy, myopathy, and cerebellar and cerebral degeneration may all appear as remote effects of an underlying malignancy. The more atypical or complex the signs and symptoms, the greater the chance that cancer is associated. Certain features of polymyositis associated with malignancy should be emphasized. With rare exceptions, all these patients will be over 40 years of age and most will have skin changes typical of dermatomyositis, although perhaps not as florid as the typical case. Particularly striking in this group is the acute onset of symptoms, although there is no apparent correlation between the intensity of skin or muscle changes and evidence of widespread metastatic disease. The therapeutic response to corticosteroids is generally poor in contrast to polymyositis without associated cancer. The tumor is usually a carcinoma, most particularly of the breast, ovary, uterus, stomach, and lung. Most of the time the polymyositis precedes discovery of the tumor, but the two conditions may clinically occur simultaneously, or the tumor may antedate the polymyositis.

The myasthenic syndrome (Lambert-Eaton syndrome) is usually associated with oat cell carcinoma of the lung. Patients complain of weakness of proximal muscles, especially of the pelvic girdle. Oculobulbar involvement is uncommon. Diagnostic of this condition is a peculiar tendency of strength to increase over several seconds of sustained contraction, and this phenomenon may be demonstrated by electromyographic studies.

Unusual vascular syndromes occasionally herald the presence of cancer particularly in the elderly, whose circulatory status is often marginal. For example, peripheral gangrene secondary to the presence of circulating cryoglobulins or cryofibrinogens may occur even before the tumor can be diagnosed by the usual clinical and laboratory procedures. Chronic disseminated intravascular coagulation manifested as purpura, gangrene, or a series of cerebrovascular accidents may also be an early feature of malignancy.

Therapy for the cancer patient should not be a one-sided decision but rather should be a product of discussion with experts from all modalities of treatment, including surgery, radiation therapy, and chemotherapy. It is obvious to the oncologist that the initial therapeutic regimen for the patient holds the greatest potential for cure, prolonged survival, or palliation and should therefore be optimal in the best sense of the word. Throughout the care of the cancer patient, the physician should adopt a policy of openness and honesty, combined with optimism and a readiness to help.

An overview of the most important malignancies in the elderly, based on mortality figures, follows. Attention is directed to differences in therapeutic regimens in this group where such information is available.

CANCER OF THE PROSTATE

Prostate cancer is primarily a disease of middle and old age and is the most common tumor encountered in patients beyond 80 years of age. Although many of these tumors are cured by transurethral resection or by radical prostatectomy, the majority of patients have advanced disease at the time of diagnosis, as evidenced by bone scanning or by bipedal lymphangiography. The serum acid phosphatase level correlates well with tumor volume: an abnormally high acid phosphatase generally indicates metastatic spread to bones and other sites. For precise staging, the bone marrow acid phosphatase is most sensitive and reflects the presence of metastatic tumor cells which may not be detectable by any other means. Determination of the carcinoembryonic antigen (CEA) may also be of benefit in staging and in correlation with response to therapy.

The mainstay of therapy in disseminated prostate cancer is endocrine manipulation. The value of bilateral orchiectomy and oral estrogens such as diethylstilbestrol (DES) is well established for the relief of bony pain and decrease in the metastatic spread of the tumor. The extensive Veterans Administration studies have indicated, however, that such therapy is only palliative and is best reserved for the symptomatic phase of the patient's disease: the length of survival is not reduced by delayed endocrine manipulation. The Veterans Administration studies further pointed out the high incidence of cardiovascular disease with conventional daily doses of DES of 5 to 15 mg.[2] It was subsequently shown that administration of DES at 1 mg daily produced the same antitumor effect seen with higher doses of the drug and was associated with a lower incidence of cardiovascular deaths. The role of ablative procedures such as hypophysectomy or bilateral adrenalectomy is uncertain; a review of the literature indicates a brief response in about 50 per cent of cases.

It is anticipated that measurement of the level of androgen receptor sites in primary or metastatic tumor will aid in determining which patients are more likely to benefit from endocrine manipulation. A useful new compound in patients resistant to hormonal therapy is Estracyt, an estradiol-nitrogen mustard combination, currently undergoing extensive clinical trials.

Relief of pain may be obtained by endocrine manipulation or by judicious administration of select analgesics. Indomethacin, by a poorly understood mechanism of action, often relieves bony pain when given orally in daily divided doses of 100 to 200 mg. Administration of intravenous courses of radioactive phosphorus (P^{32}) with or without priming regimens of testosterone or parathormone may allow striking and long-lasting relief of skeletal pain in roughly two thirds of patients. In a pilot study at Walter Reed General Hospital, cholestyramine also was shown to relieve bony pain, perhaps by its hypocholesterolemic effect on the tumor. Cytotoxic chemotherapy with cyclophosphamide and 5-fluorouracil has allowed objective responses in as high as 40 per cent of patients. Mithramycin is useful not only for lowering an elevated serum calcium but also for relieving bony pain.

CANCER OF THE LUNG

The outlook for patients with cancer of the lung is poor, with overall 5 year survival rates of about 5 to 7 per cent. Mass roentgenographic screening of high risk patients has generally failed, but the combination of frequent screening sputum cytologies and chest x-rays at 3 or 4 month intervals may allow earlier detection and resection of some of these tumors. Certainly, in experienced hands, with the use of multiple sputum specimens, 70 to 95 per cent of all lung cancers can be diagnosed by cytology alone. The use of fiberoptic bronchoscopy and brush biopsy has further increased the yield of early detection. Tumor markers, such as "big ACTH,"[1] are being studied for their role in early diagnosis.

Mediastinoscopy has virtually supplanted scalene node biopsies for an assessment of resectability. Unfortunately, less than 25 per cent of all patients are eligible for resection at the time of diagnosis. Oat cell carcinoma is of a special nature, because it is almost always widely disseminated at the time of diagnosis, thus precluding surgical intervention.

If the patient has an unresectable tumor, radiotherapy given to the primary site and encompassing hilar and mediastinal adenopathy will help to prevent complications such as bronchial obstruction and infection, pain, and hemoptysis. There is a special role for preoperative radiotherapy in the management of superior sulcus tumors, generally of the epidermoid type, which often have a fair to good prognosis.

A review of the chemotherapy of lung cancer indicates a significant difference in response rate to various drugs depending on the histologic cell type; e.g., useful drugs include nitrogen mustard, CCNU, and adriamycin for squamous cell carcinoma, methyl-CCNU and methotrexate for adenocarcinoma, procarbazine for large cell carcinoma, and a host of drugs for oat cell carcinoma. The latter is by far the most responsive type of tumor to chemotherapy, probably because of its rapid cellular kinetics. Hansen et al.[4] have aggressively treated advanced lung cancer with combination chemotherapy and x-irradiation to the primary tumor; a significant prolongation in survival in the responding group was observed. Combination chemotherapy is particularly efficacious against oat cell carcinoma, e.g., cyclophosphamide—Oncovin—prednisone—procarbazine (COPP) or cyclophosphamide—Oncovin—methotrexate, with impressive response rates exceeding 50 per cent and a definite prolongation in survival. Further studies along this line are indicated. The use of high-dose methotrexate intravenous infusions followed by Leukovorin for reversal of systemic toxicity has yielded a high response rate and is being further investigated.

CANCER OF THE BREAST

The overall 5 year survival of patients with cancer of the breast remains at about 50 per cent. Roughly two thirds of all women with breast cancer develop disseminated disease during their lifetime. In patients who have involvement of axillary nodes, the median time to tumor recurrence is 3 years. It is hoped that early detection by self examination and by certain technical procedures will improve overall survival. Xeroradiography, thermography, and mammography have been utilized in screening centers; lesions averaging 1 cm in diameter can be picked up with these techniques. Such small primary tumors are associated with metastases in roughly only 30 per cent of cases. It is particularly important to screen such high risk groups as patients with fibrocystic disease, nipple discharge, history of benign or malignant breast tumors, family history of breast cancer, and a past history of uterine cancer.

In nearly every published series, the results of radical mastectomy have been superior when this procedure has been used consistently.[9] It remains to be proven that lesser surgical procedures such as simple mastectomy, alone or followed by x-irradiation, are as efficacious as radical mastectomy. More than half the breasts removed for cancer have multiple foci of tumor; synchronous cancers have been found in up to 20 per cent of random biopsies done on the opposite breast, particularly carcinoma of the lobular type. In fact, some authors recommend a contralateral prophylactic subcutaneous mastectomy in all females with lobular carcinoma. Axillary lymph nodes must be carefully examined for the presence or absence of tumor involvement; there is a 35 per cent error in evaluating the axilla clinically. Routine postoperative radiotherapy does not increase the rate of survival but does appear to decrease the incidence of local recurrence.

Endocrine manipulation is assuming a greater role in the management of advanced breast cancer. It is recognized that breast cancer is composed of several clones of cells that have different growth and biochemical characteristics. Hormone therapy may thereby affect one or more clones but not necessarily all, and a partial response or a complete response of short or long duration may occur. Combination chemotherapy might be used in addition to attack those cellular clones not responsive to endocrine manipulation.

An assay for the level of estrogen receptors in the primary tumor or its metastases will allow for a sensible judgment regarding the tumor's ability to respond to some form of endocrine manipulation. In estrogen target tissues and hormone-dependent tumors, the steroid enters the cell and binds to a cytoplasmic protein called the estrogen receptor. The steroid-receptor complex then migrates to the nucleus where it initiates biochemical events characteristic of estrogen stimulation. Of tumors with a positive or high level of estrogen receptor, 55 to 60 per cent will respond to endocrine treatment. It has also been noted that the longer the free interval from initial treatment to the first tumor recurrence, the greater the probability of a significant remission after an ablative endocrine procedure.

Diethylstilbestrol at a dosage of 15 mg daily has been useful primarily in controlling soft tissue disease. Androgens, such as fluoxymesterone at a dosage of 30 to 50 mg daily, are also useful in the treatment of patients with soft tissue disease and may be of benefit in patients with bone disease by relieving pain and allowing recalcification of lytic areas.

Either bilateral adrenalectomy or hypophysectomy in postmenopausal women with recurrent or metastatic breast cancer results in a 35 to 50 per cent response rate overall, a higher response rate being seen in patients who had previously responded to estrogens or androgens. Aminoglutethimide may produce a "medical adrenalectomy" by a reversible inhibition of the enzymatic conversion of cholesterol to pregnenelone, a step required for the biosynthesis of all adrenal steroid hormones, including estrogens. Tumor responses have been seen in patients with advanced breast cancer, and further clinical trials are in progress.

Indomethacin, at a dosage of 150 to 200 mg daily in divided doses, has been shown to be useful in relieving bony pain. L-DOPA[6] can also relieve bony pain by suppressing serum prolactin levels. If the bone pain is markedly relieved, these patients have an increased chance of response to some form of endocrine ablative procedure. The L-DOPA test seems to correlate well with estrogen receptor studies.

The use of chemotherapy has added greatly to the control of advanced breast cancer. Generally, a combination of active agents is used, such as cyclophosphamide-methotrexate-5-fluorouracil, allowing for a 60 to 70 per cent response rate and a median duration of response of 8 months. The use of Alkeran in an adjuvant fashion in patients with positive axillary nodes after surgery produced a decrease in tumor recurrence rate in both premenopausal and postmenopausal patients. An even more pronounced decrease in tumor recurrence has been noted with prolonged combination chemotherapy using cyclophosphamide, 5-fluorouracil, and methotrexate; after 27 months of study, treatment failure occurred in 24 per cent of 179 control patients and 5.3 per cent of 207 women given combination chemotherapy.[3] These results suggest that many more women can be cured with a combination of surgery and chemotherapy. Adriamycin is a new antitumor agent with striking effectiveness against breast cancer, allowing responses in up to 45 per cent of cases. Adriamycin may be most effective in the 10 years plus postmenopausal patient with a long disease-free interval and soft tissue disease. In one study, a combination of cyclophosphamide and adriamycin produced an 80 per cent response rate with a median duration of response of 10 months.[5]

COLON AND RECTAL CANCER

The incidence of colorectal cancer is increasing in the United States, with over 80,000 new cases diagnosed and over 50,000 deaths each year, representing about 15 per cent of all malignant neoplasms.

Rectal bleeding, a change in bowel habits, and abdominal pain are the most frequent presenting signs and symptoms. The blood is usually mixed with the stool and should not be ascribed simply to the presence of hemorrhoids. Right-sided neoplasms tend to be larger, fungating, and more friable with a tendency to bleed, as opposed to left-sided tumors which are more scirrhous and obstructive early in the course of the disease. These differences are related to the caliber of the colonic lumen and to the consistency of the feces at these two sites. Rectal carcinoma often presents with bleeding, tenesmus, and a change in caliber of the stool. There is usually an increase in frequency, with a particular need to defecate upon arising in the morning. Abdominal pain secondary to colorectal tumors is usually a late symptom and may mimic any of a variety of abdominal disorders. Before chronic cholelithiasis is accepted as an explanation for abdominal pain, a full barium study of the bowel is indicated.

There are several diagnostic methods which, if diligently applied, will undoubtedly increase the cure rate for these patients. Frequent determination of occult blood in the stool is not an optimal screen; a high percentage of false-positive results occur unless the patient has been on a meat-free diet for several days. Exfoliative cytology is frequently positive, though cumbersome, and probably adds little to roentgenographic and endoscopic studies. Digital examination of the rectum and proctosigmoidoscopy are the first procedures of choice and will serve to detect roughly two thirds of all cancers of the large bowel. The rectum and sigmoid colon cannot be evaluated dependably by the barium enema. The flexible fiberoptic colonoscope is useful for visualization of the entire large bowel with biopsy of suspicious areas. Although routine proctoscopy is of value in families with multiple polyposis and in patients with ulcerative colitis, its value in asymptomatic patients has not yet been established.

Many adenocarcinomas of the colon and rectum arise from adenomatous polyps, predominantly those polyps greater than 1.5 to 2.0 cm in diameter. It is generally recommended that all polyps within reach of sigmoidoscopy should be excised regardless of size. The larger polyps (over 1.5 to 2.0 cm in diameter) are associated with at least a ten-fold increase of carcinoma and should be excised in the patient who is in good condition even if laparotomy is necessary. If the stalk of the polyp has been invaded at its base by carcinoma, then the risk of dissemination is high and a standard cancer operation must be performed.

The primary treatment of adenocarcinoma of the colon is surgery. A hemicolectomy with as complete resection of the cancer-bearing bowel segment as possible is performed. Prophylactic bilateral oophorectomy may be indicated, especially in postmenopausal women, since metastatic tumor in the ovaries occurs in a significant number of these patients. Adenocarcinoma of the rectum is treated by an anterior or anteroposterior resection, depending on the distance of the tumor from the anal verge. Preoperative radiotherapy for rectal cancer has improved survival rates in several series. A significant reduction in the incidence of positive regional nodes has been noted following preoperative radiotherapy of cancer of the sigmoid colon and rectum. Preoperative radiotherapy may also improve the resectability rate by decreasing the tumor bulk. Postoperative radiotherapy of colorectal cancer may offer significant palliation in nonresectable cases. Palliative resections are indicated to relieve obstruction, hemorrhage, and rectal drainage, even in the presence of liver and lung metastases. "Second look" surgery in colorectal cancer has been useful in determining the extent of residual tumor and its resection where possible.

A useful biochemical test in following the course of disease is the carcinoembryonic antigen (CEA) test. CEA is a glycoprotein present in a wide variety of carcinomas that is similar to antigens normally present in the fetal circulation. The specificity of the test is hampered by the fact that the antigen is present in a variety of benign disorders, including heavy smoking, alcoholic cirrhosis, and ulcerative colitis. However, malignant may be differentiated from nonmalignant processes in part by the amount of CEA in the serum. A negative assay does not exclude the diagnosis of early cancer, although it makes highly unlikely the diagnosis of widespread metastatic cancer. Preoperatively, undetectable CEA in a patient with known colonic cancer suggests a localized tumor with a good prognosis. An elevated CEA in such patients correlates with metastatic disease and a poor prognosis. Postoperatively, an elevated CEA usually indicates residual or metastatic tumor. Serial serum CEA determinations have some value in following the course of gastrointestinal cancer after surgery or chemotherapy, but interpretation of results must be made in the context of the overall clinical picture.

Over the past 20 years, survival statistics compiled by the American Cancer Society have indicated little change in the 5 year survival (approximately 35 per cent) of patients who have been operated upon for curative resection of colorectal carcinoma, particularly when nodal metastases were present. The results with chemotherapy have generally been poor. In no reported study has it been clearly demonstrated that 5-fluorouracil or any other drug can prolong survival in patients with advanced colorectal cancer. The patient with more clinically indolent disease, as evidenced by a longer interval from the diagnosis of the primary lesion to diagnosis of recurrent or metastatic disease, appears more likely to respond than the patient with a more aggressive tumor. Combination chemotherapy results have generally been no better than those seen with 5-fluorouracil alone. However, Moertel et al.[8] recently compared methyl-CCNU, 5-fluorouracil and vincristine with 5-fluorouracil alone. The three drug combination gave a response rate of 43.5 per cent versus 19.5 per cent with 5-fluorouracil. Infusion of 5-fluorouracil into the hepatic artery for control of liver metastases has produced objective response rates exceeding 50 per cent in several series. Moreover, there is often prolongation in survival over patients treated with conventional systemic therapy. The complications of hepatic infusion, including liver damage and failure, septicemia, arterial occlusions, hemorrhage, and catheter leakage have limited the usefulness of this mode of therapy.

Cancer of the Uterine Endometrium

Although adenocarcinoma of the uterine endometrium classically occurs in postmenopausal, obese, hypertensive, diabetic women who have been infertile and had a late menopause, patients may exhibit all, several, or none of these characteristics. Abnormal uterine bleeding is the most common sign of uterine cancer.

Prolonged estrogen stimulation appears to play a primary role, and its unopposed action may result in adenomatous hyperplasia transforming into carcinoma in situ and eventually invasive adenocarcinoma of the endometrium. Recent studies[10,12] indicate that exogenous estrogen therapy is associated with an increased risk of endometrial carcinoma and may indeed have an etiologic role. In these studies the risk of uterine cancer was increased 5 to 14 times in women taking estrogens. Precise guidelines for the use of estrogens in postmenopausal patients are lacking since the effect of estrogen dosages, specific estrogens, or treatment schedules are unknown. There is no question, however, that these women should be followed very closely for the development of endometrial carcinoma.

The overall 5 year survival for patients in all stages ranges from 45 to 75 per cent. Hysterectomy alone is effective treatment for stage I endometrial cancer (tumor confined to corpus), which is moderately well differentiated and invades less than half the uterine wall. A combination of radiotherapy and surgery gives the best survival rates when the tumor is anaplastic or deeply invasive. Radiotherapy significantly reduces both vaginal and pelvic recurrences. More advanced tumors may be treated by radical surgery, radiotherapy alone, or by radiotherapy and surgery in combination. The latter approach allows removal of the primary tumor and detection of lymph node metastases in areas not usually encompassed by radiotherapy portals. Whether operative resection of large nodal metastases increases survival rates is not known.

Hormone therapy with progesterone is generally offered to patients with advanced or recurrent disease. Overall response rates are 30 to 35 per cent. A more favorable response is seen in patients with well differentiated or slowly growing tumors in which long periods have elapsed between initial therapy and the onset of recurrent or metastatic disease. Objective responses are generally seen within 2 to 3 months of instituting treatment, and the drug should be continued as long as an objective response is maintained. Depo-medroxyprogesterone acetate (Depo-Provera), hydroxyprogesterone caproate (Delalutin) and megestrol acetate (Megace) are progesterone compounds used in endometrial carcinoma and appear to be equally effective. When response to a progestational agent fails, an increase in dosage of drug or a change to a different form of progesterone may be useful. Adding cytotoxic chemotherapy such as an alkylating agent to the progesterone may induce an additional remission.

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Coney Island Hospital
2601 Ocean Parkway
Brooklyn, New York 11235

Immune Responsiveness and Hematologic Malignancy in the Elderly

Gloria Fernandez, M.D., and Joel M. Schwartz, M.D.***

Normal immune function decreases markedly with age whereas autoimmunity and cancer increase. Clinical and experimental data suggest that the events are probably related, although the nature of the relationship is not yet known. This article will review the effects of aging upon immune responsiveness, the role of immunologic reactions in modifying the growth of tumors, and, finally, some recent observations on the origin, natural history, and prognosis of hematologic malignancies in the elderly.

THE NORMAL IMMUNE RESPONSE

The normal immune response in man is mediated by the interaction of three types of cells: mononuclear phagocytes, thymus-dependent or T lymphocytes, and bursa-equivalent or B lymphocytes.

Mononuclear phagocytes in the blood (monocytes) and tissues (macrophages, histiocytes) have a role in the initial processing of antigen for presentation to T and B cells as well as in the expression of both cellular and humoral immunity. Their phagocytic capacities are enhanced by surface receptors for the Fc fragment of immunoglobulin (Ig) and the third component of complement (C3) which confer such functional properties as immune adherence and opsonization and which augment the ability of mononuclear phagocytes to dispose of foreign antigens: e.g., bacteria coated with antibody or with antibody and complement. Mononuclear phagocytes enhance the immunogenicity of the ingested antigen, perhaps through a metabolic process, or by attachment of an RNA strand,[55] and present the processed antigen to T and B cells. Tissue macrophages are present in all the regions of the peripheral lymphoid organs. They are most conspicuous in the subcapsular and medullary sinuses of the lymph nodes (Fig. 1) and in the Billroth cords of the spleen.

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*Director of The Blood Bank, Coney Island Hospital; Instructor in Medicine, State University of New York Downstate Medical Center, Brooklyn, New York.

**Chief of Hematology, Coney Island Hospital; Clinical Associate Professor of Medicine, State University of New York Downstate Medical Center, Brooklyn, New York.

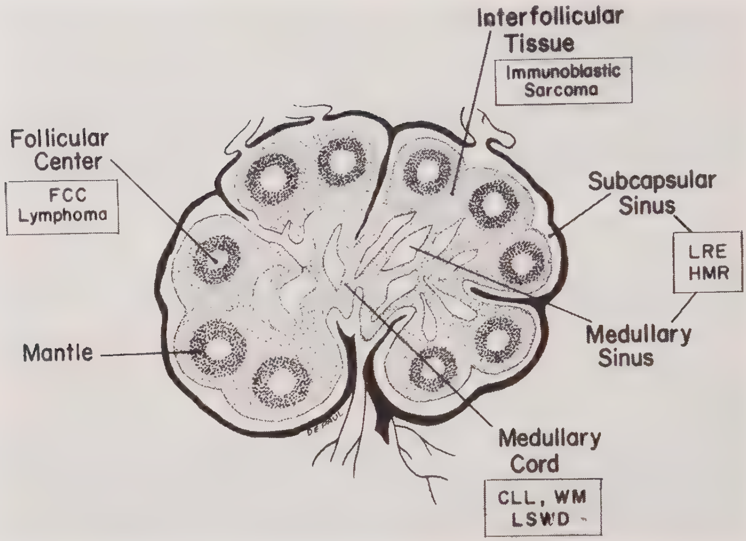

Figure 1. Relationship between the topography of the normal lymph node, the functional compartments of the lymphatic system, and the presumed sites or origin of lymphoreticular tumors. B cells are concentrated in the centers of the follicles and in the medullary cords; T cells predominate in the interfollicular tissues. Follicular center cell lymphomas (cleaved and noncleaved) and immunoblastic sarcoma are thought to originate, respectively, from B cells at the center of the germinal follicles and B cells in the interfollicular tissues. Chronic lymphocytic leukemia (CLL), well-differentiated lymphosarcoma (LSWD), and Waldenström's macroglobulinemia (WM) have surface characteristics which suggest their origin from B cells of the medullary cords (see text). Histiocytic medullary reticulosis (HMR) and some cases of leukemic reticuloendotheliosis (LRE) are neoplasms of true histiocytes such as those which line the medullary and subcapsular sinuses. The cytogenesis of the malignant cells in Hodgkin's disease is uncertain.

The lymphocytes include two major functional categories; both derive from precursor cells present in the bone marrow. One group, the T cells, undergoes maturation and structural change within the thymus before reaching its ultimate location in the peripheral lymphoid tissues. The other group, the B cells, undergoes a parallel process in the bursa of Fabricius in birds and in an equivalent unidentified organ in mammals.

Antigenic stimulation of T lymphocytes results in the production of subpopulations of cells and of soluble lymphokines which are essential for the full expression of cell mediated immune responses (Table 1). Among the cells produced are (1) helper cells which augment production of antibody by B cells, (2) suppressor cells which decrease the production of antibody by B cells and which regulate B and T cell reaction to antigens, including autoantigens, and (3) killer cells which have a role in the rejection of foreign grafts and in the destruction of tumor cells. The B cells, recognizable as plasma cells in their fully mature forms, are involved mainly in the production of the circulating antibodies which mediate humoral immune responses (Table 1). However, some antibodies influence certain cellular immune reactions by their action as autoantibodies directed against T cells[59] and by other poorly understood means.

Table 1. *Cell-Mediated and Antibody-Mediated Immune Reactions*

CELL-MEDIATED (T CELL) IMMUNE REACTIONS
- Delayed hypersensitivity responses to intracutaneous injection of foreign antigens
- Rejection of homografts
- Graft versus host disease
- Protection against intracellular organisms: viruses, acid-fast bacilli
- Destruction of tumor cells by specific cytotoxic lymphocytes
- Thyroiditis secondary to direct immune injury of thyroid tissue by autoimmunized cytotoxic lymphocytes (Hashimoto's thyroiditis)

ANTIBODY-MEDIATED HUMORAL IMMUNE REACTIONS
- Arthus reaction
- Systemic anaphylaxis
- Neutralization of circulating viruses and encapsulated bacteria
- Antibody-dependent destruction of tumor cells by non-immune lymphocytes and mononuclear phagocytes
- Autoimmune hemolytic anemia secondary to attachment of antibodies and often complement to erythrocytes and subsequent removal of the sensitized erythrocytes in the spleen or by intravascular lysis
- Immune complex disease: e.g., glomerulonephritis secondary to attachment of anti-DNA-DNA immune complexes and complement to glomerular basement membrane (systemic lupus erythematosus)

The T and B lymphocytes circulate in the blood and "home" to different areas in the lymphoid organs. Thus T cells filter in and out of the interfollicular tissues of the lymph nodes and the periarteriolar sheaths of the spleen. B cells distribute to the follicular centers of the lymph nodes and spleen and the medullary cords of the lymph nodes (Fig. 1).[12] T and B cells are further distinguished by characteristic surface markers, some of which are detected by the use of specific immunologic reagents and techniques.[7] Whereas the T cells have receptors for sheep erythrocytes and are destroyed by anti-human thymocyte serum, the B cells synthesize easily detected surface Ig and have surface receptors for C3 and for Fc fragments of IgG. As previously noted, mononuclear phagocytes also possess surface receptors for the Fc fragment and they may therefore attach IgG nonspecifically. They are distinguished from B cells by their phagocytic capacity, their inability to synthesize the IgG surface marker, and by the differential reactivity of their Fc receptors (Table 2).

The application of immunologic techniques to the enumeration of circulating mononuclear cells indicates that about 50 to 70 per cent of the cells are T cells, 10 to 25 per cent are B cells, 5 to 15 per cent are monocytes, and the remainder are null lymphocytes. The distribution of mononuclear cells in normal lymph nodes is similar to that in the peripheral blood with a predominance of T cells over B cells.[7]

EFFECTS OF AGING ON THE IMMUNE SYSTEM

Age-related changes in the structure and the function of the immune system occur throughout life.[22,37] Except for a temporary sharp increase in the size and the weight of the human thymus between ages 55 and 60,

Table 2. *Markers on the Surface of Lymphoreticular Cells*

	T CELLS	B CELLS	MONONUCLEAR PHAGOCYTES
Human T cell antigen	+[a]	0	0
Sheep red blood cell receptor	+[b]	0	0
Complement component receptor (C3)	0	+[c]	+[c]
IgG Fc receptor	0	+[d]	+[d,e]
Surface-bound Ig	0	+	±[f]

[a] Cell destroyed by antithymocyte serum
[b] Cell binds nonsensitized sheep erythrocytes
[c] Cell binds erythrocyte-IgM antibody-complement complex
[d] Cell binds aggregated IgG
[e] Cell binds erythrocyte-IgG antibody complex
[f] Cell may attach IgG non-specifically through Fc receptor. After removal of IgG with trypsin, cell not able to synthesize surface Ig

the thymus involutes progressively beginning with puberty; involution affects mainly the cortex. The weight of the human spleen begins to decrease at age 65 and that of the human tonsils at age 70. The involution in these organs is due mainly to depletion of lymphocytes and is accompanied by a parallel process throughout the lymph node system. Studies of circulating lymphocytes suggest that T cells are depleted whereas the proportion and possibly the absolute number of B cells increase.[13,14]

T and B cell functions decline in the elderly; the T cell impairment is more profound. The in vitro response of T cells to plant mitogens and allogeneic lymphocytes, and the skin test reactions to PPD, DNCB, and other antigens are all decreased in older as compared to younger patients.[14,37] Similarly, there is considerable decline in the titer and avidity of antibody produced by B cells in primary and secondary immune responses.[22] Since the capacity to synthesize IgG declines more sharply with age than the capacity to synthesize IgM, the inability to sustain IgG antibody production might reflect functional deficiency of helper T cells.[47] As far as is known, there is no loss of mononuclear phagocytic function during aging, but the data which bear on this point are limited. The phagocytic capacity and the lysosomal enzyme activity of macrophages in mice are not affected by age.[25]

The frequent occurrence of autoimmune manifestations in the elderly (e.g., autoantibodies, pernicious anemia, autoimmune hemolytic anemia secondary to lymphoma),[14,22] in patients with immune deficiency,[21] and in animals undergoing thymectomy in the neonatal period[22] is consistent with the hypothesis that thymic function may normally have a role in the suppression of B and T cell reactions to autoantigens. An alternative hypothesis suggests that the high incidence of autoimmune phenomena in the elderly reflects entry of or exposure to forbidden antigens: e.g., viruses[21] and tumor antigens.[17] Having gained access to the immune system, they presumably induce the formation of (1) effector T cells or specific antibodies that cross-act with host antigens, or (2) complexes of antigen, antibody, and complement which attach to cell surfaces and initiate inflammatory or destructive reactions. The increased incidence of autoimmune manifestations in patients with deficiency of secretory IgA is consistent with this hypothesis. Lack of IgA presumably predisposes to excessive exposure to antigens derived from the gut.

The decline of immunologic function with aging may relate not only to the increased frequency of autoimmune phenomena but, possibly, to the increased incidence of malignancy in the elderly. The remarkable increase in the incidence of malignancy in the immunosuppressed recipients of kidney transplants,[28] in patients with immune deficiency diseases,[33] and in thymectomized animals exposed to oncogenic viruses[22] is frequently cited as evidence in favor of an immunologic surveillance mechanism as proposed originally by Thomas and by Burnet. Although the existence of an immune mechanism for the destruction of incipient cancer is commonly supposed, Bentley[5] and Schwartz[53] have recently raised several important objections. Only one of these will be cited here. Immune surveillance theory predicts that the frequency of *all* cancers will increase as immune functions fail. However, the majority of malignancies in immunodeficient individuals are of lymphoid origin. This may indicate that perturbation within the lymphatic system itself—such as failure to terminate reactive proliferation triggered by antigen—is important in the pathogenesis of the lymphoid tumors. Indeed, lymphoid malignancy, immune deficiency, and autoimmunity might each represent different aspects of the same underlying defect of the lymphatic system without any of the three being a primary event.[17,53]

ROLE OF IMMUNE REACTIONS IN MODIFYING TUMOR GROWTH

Although controversy surrounds the concept of an immune surveillance mechanism which eliminates neoplastic cells as they arise, there is no question that tumors, once established, elicit both cellular and humoral responses to tumor-associated antigens. These immune responses, in particular those mediated by cells, seem to have an important role in determining prognosis and the response to therapy. Patients who display vigorous specific tumor immunity at the onset of malignant disease and who recover immune function rapidly after cessation of therapy frequently have a relatively good prognosis, whereas patients with weak or absent responses fare poorly.[27]

The immune destruction of tumor cells is accomplished by means of several well-defined processes;[4,26,40] others undoubtedly exist. The first category of reaction involves killer T lymphocytes which destroy tumor cells directly upon contact with surface antigen; no antibody is involved. The exact mechanism of the cytotoxicity is unknown. Soluble factors released by the killer cells, including a cytotoxic factor, and a factor which attracts macrophages may play a role. In a second mechanism, tumor cells are sensitized by a specific antibody. Lymphocytes and mononuclear phagocytes attach the Fc portion of the tumor antibody through their Fc receptor and thereby acquire the ability to destroy the sensitized tumor cell. The lymphocyte which participates in antibody-dependent cellular cytotoxicity reactions is not fully identified. The final mechanism involves cytotoxic antibodies directed against surface antigen which activate the full complement sequence. The tumor cells are lysed without any involvement of lymphocytes or mononuclear cells.

The serum of some patients with widespread malignancy contains factors which protect tumor cells from destruction by cytotoxic lymphocytes.[26] The serum factors consist of (1) tumor antigens shed by the growing neoplasm which circulate as such or as complexes with antibody, and (2) antibodies which enhance the growth of tumor. The protection afforded the growing tumor by these serum factors is presumably explained by their ability to block reaction sites on the killer T cells and the target tumor cells. (Antibodies capable of counteracting the tumor-protecting activity of blocking factors have been demonstrated in the serum of patients who have achieved remission of their disease.[26]) Failure to contain the growth of malignancy can be further ascribed to tumor-induced activation of suppressor T cells which results, in turn, in suppression of the antibody-dependent cytotoxicity of macrophages.[20]

Advancing cancer may be associated not only with impaired immune destruction of tumor cells, but also with a general decline in immune competence which is due to a variety of poorly defined factors. Among these are poor nutrition, inhibitory serum materials released from tumor cells or from other tissues under the influence of factors produced by the tumor, the stresses of anesthesia and surgery, and the effects of radiotherapy and chemotherapy.[27] Malignant transformation of the lymphocytes per se may also influence immune competence. Defects in immune function encountered in patients with certain neoplastic diseases are summarized in Table 3 and will be alluded to in the section on hematologic malignancy. The definition of the scope and nature of the immune deficiencies in cancer as well as therapeutic manipulations aimed at restoring immune competence constitute areas of active investigation. The subject of immunotherapy has recently been reviewed.[56]

HEMATOLOGIC MALIGNANCIES IN THE ELDERLY

The hematologic malignancies can be broadly separated into proliferation of cells of lymphoreticular origin (lymphoid neoplasms) and of cell types indigenous to the bone marrow (myeloid neoplasms). The lymphoid neoplasms commonly encountered in the elderly include (1) nodular and diffuse forms of lymphocytic lymphoma (lymphosarcoma) and histiocytic lymphoma (reticulum cell sarcoma), (2) chronic lymphocytic leukemia, (3) Waldenström's macroglobulinemia, (4) benign and malignant proliferations of plasma cells, and (5) Hodgkin's disease of the mixed cellularity and lymphocyte depletion types. The common myeloid neoplasms include polycythemia vera, myelofibrosis and myeloid metaplasia, and acute myelocytic leukemia.

Table 3. *Cellular and Humoral Immune Functions in Various Malignancies*[24,27]

	CELLULAR IMMUNITY	HUMORAL IMMUNITY
Hodgkin's disease	Substantial impairment in advanced stages[a]	Modest impairment in advanced illness
Lymphocytic and histiocytic lymphomas in adults[b]		
Nodular	Intact	Intact
Diffuse	Impaired in advanced stages of aggressive disease	May be impaired in advanced stages of aggressive disease
Chronic lymphocytic leukemia	Normal or near normal	Substantial impairment[c]
Multiple myeloma	Near normal	Impaired[d]
Acute myelocytic leukemia	Impaired in some patients[e]	Normal or near-normal
Chronic myelocytic leukemia	Intact	Intact
Solid tumors	Variable[f]	Variable[f]

[a] Absolute depletion of T cells is major factor; T cell dysfunction also implicated.

[b] See Table 4 and text for equivalent entities in functional classification of lymphomas.

[c] Large accumulation of immunoincompetent B cells; very small number of residual normal B cells.

[d] Production of Ig by normal B cells is suppressed by macrophages[6]

[e] Cellular (and humoral) immunity suppressed further by intensive chemotherapy. Impaired cellular immunity before treatment, failure to recover normal function upon achieving remission, or loss of normal function during remission may imply poor prognosis.

[f] Immunodeficient patients show greater impairment of cellular than humoral immunity. Not all patients are immunodeficient.

LYMPHOID NEOPLASMS

Recent ultrastructural, cytochemical, and, especially, immunologic studies of lymphoid neoplasms have yielded a new understanding of their nature and origin, and have stimulated attempts to reclassify lymphoid tumors in terms of their relationship to the functional (B and T) compartments of the lymphatic system.[7] The discussion which follows, the functional classification given in table 4, and the relationships illustrated in figure 1 represent our attempt to synthesize the views of a number of investigators. Our discussion refers extensively to a functional-morphological classification of non-Hodgkin's lymphomas proposed recently by Lukes and Collins[35,36]; table 4 permits comparison of certain tumor entities defined by these authors and entities described by others which may be more familiar. Retrospective analysis of 226 patients reclassified according to the functional scheme of Lukes and Collins has shown that the scheme correlates well with the natural history and prognosis of stage I and stage II disease.[10] Data to be obtained prospectively from a large number of patients staged and treated according to the newer methods will be necessary to establish the predictive value and the full clinical relevance of this approach.

Non-Hodgkin's lymphomas in adults are mainly of B cell origin: i.e., nodular lymphoma,[2,18,31,54] most cases of diffuse lymphoma[2,9,18] and of chronic lymphocytic leukemia,[1,6,44,50] and Waldenström's macroglobulinemia.[44] Multiple myeloma is also a B cell neoplasm. T cell lymphomas in adults and neoplastic proliferations of true histiocytes, on the other hand, are decidedly less common. Indeed, T cell neoplasms in adults are largely limited to those which involve the skin widely (e.g., mycosis fungoides and Sezary syndrome)[8,16] and to exceptional cases of diffuse lymphoma[18,30] and chronic lymphocytic leukemia.[57] The proliferations of true histiocytes include two relatively rare disorders: histiocytic medullary reticulosis (malignant histiocytosis)[30] and some cases of leukemic reticuloendotheliosis (hairy cell leukemia).[29,30] The cytogenesis of the malignant cells in Hodgkin's disease is uncertain. Figure 1 illustrates the relationship between the functional compartment of origin of non-Hodgkin's lymphomas and the topography of the normal lymph node.

Follicular Center Cell Lymphoma

Lukes and Collins[35,36] observed that the prominent cell types in the follicular centers of normal and reactive lymph nodes correspond morphologically to a continuum of cell types formed in vitro when small peripheral blood lymphocytes are stimulated with mitogens. On the strength of these observations and the known importance of follicles for humoral immune competence, they proposed that the centers of lymph node follicles were sites of normal transformation of small B lymphocytes stimulated by antigen. The first stage of transformation involved nuclear cleavage. This was followed by progressive enlargement of the cells to four or more times their original size through the acquisition of cytoplasm and the gradual growth of the nucleus, loss of nuclear cleavage, and the appearance of prominent nucleoli (reference 36, figures 1 and 2). Whereas the cleaved cells in the centers of the follicles did not divide or divided very slowly, the large noncleaved cells divided rapidly and seemed to move through the lymphocyte mantle into the interfollicular tissues. Called immunoblasts in this location, the large transformed cells either proliferated as such or they gave rise to the plasma cells and the small B (memory) lymphocytes of the cortical pulp and the medullary cords. Small T lymphocytes in the interfollicular tissues also transformed when stimulated by antigen; the process was thought to parallel that of the B cells in the follicular centers but without the stage of nuclear cleavage.

Because cleaved and noncleaved cells resembling those at the center of normal follicles constitute the predominant cell species in a number of lymphomas (reference 36, figures 8 to 10), Lukes and Collins regard these tumors as having originated from follicular center cells (FCC). The *cleaved* neoplastic cells of some (but not all) FCC lymphomas retain the capacity to form follicles; the infiltrated lymph nodes display nodular histology. Although small and large cleaved neoplastic cells invade the blood often and seed B cell areas of the bone marrow and spleen, their presumed rate of proliferation is relatively low. The slow proliferation accounts, in part, for the frequent lack of symptoms in patients with cleaved FCC and equivalent lymphomas (Table 4) and—together with the responsiveness to radiotherapy or to chemotherapy with single agents or a combination of agents—for the relatively long median survival of affected patients (more than 5 years).[10] The relatively favorable prognosis relates with both nuclear cleavage and the capacity of the cleaved FCC to form follicles; the median survival approximates 10 years where the two features concur.[10] A change in the clinical course of cleaved FCC lymphoma from slowly progressive to aggressive frequently heralds the terminal stages. Sequential biopsies of lymph nodes obtained during the metamorphosis reveal the appearance of a prominent component of noncleaved neoplastic cells.

The growth pattern of tumors comprised predominantly (>25 per cent) of *noncleaved* cells* differs from that in which cleaved cells predominate. In a manner reminiscent of normal noncleaved FCC transformed by antigen, the neoplastic noncleaved cells proliferate rapidly. They infiltrate lymph nodes diffusely and exhibit partial or minimal follicularity in only a minority of cases. They give rise to constitutional symptoms and tend to form bulky coalescent masses. The median survival of patients with noncleaved FCC lymphoma is relatively short (1 to 2 years),[10] although a significant minority survive beyond this point.[52] The longer survival of a sub-population of patients with diffuse noncleaved FCC and equivalent lymphomas (Table 4) may reflect a limited extent of the disease at presentation or the selective sensitivity of the lymphoma cells to therapy. Noncleaved FCC and equivalent lymphomas are currently treated with three- and four-drug combination regimens.[39]

Immunoblastic Sarcoma

Lukes and Collins have used the term immunoblastic sarcoma to describe a diffuse lymphoma of B (or rarely T) cells which resembles large noncleaved FCC lymphoma morphologically and in its aggressive course but which originates from transformed lymphocytes in the interfollicular tissues.** This tumor, often regarded as a form of reticulum cell sarcoma, may develop in elderly patients and in patients with immune systems that are abnormal or deficient by virtue of associated disorders: e.g., Sjogren's syndrome, systemic lupus erythematosus, Waldenström's macroglobulinemia, chronic lymphocytic leukemia, immunosuppression (as in recipients of grafted organs), and congenital immunodeficiency states.

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*Depending on the relative size of the noncleaved cells and the stage of their apparent transformation, these cells are identified in the Rappaport[46] and other classifications as *undifferentiated lymphocytes*, *histiocytes*, or *reticulum cells*. The corresponding lymphomas or sarcomas are so named (Table 4).

**The cellular origin of a similar tumor in still other patients cannot be positively identified,[2,9,18] presumably because the rapidly proliferating cells lack the capacity to synthesize the relevant cell markers or have not had sufficient time.

Table 4. *Non-Hodgkin's Lymphoma in Adults:*

OLD TERMINOLOGY	RAPPAPORT CLASSIFICATION[46]		FUNCTIONAL CLASSIFICATION
	NODULAR OR DIFFUSE		B cell neoplasms
Reticulum cell sarcoma	Undifferentiated	(A)	Follicular center cell lymphoma
			Small cleaved (B,E)
Lymphosarcoma	Lymphocytic, poorly differentiated	(B)	Large cleaved (B,C,D)
			Small non-cleaved (A,B)
Recticulum cell sarcoma	Mixed lymphocytic and histiocytic	(C)	Large non-cleaved (D)
			Immunoblastic sarcoma (D)
Reticulum cell sarcoma	Histiocytic	(D)	Small lymphocyte lymphoma (CLL) (E)
Lymphosarcoma	Lymphocytic, well differentiated	(E)	Plasmacytoid lymphocyte lymphoma (Waldenström's)
			T cell neoplasms
			Immunoblastic sarcoma (D)
			Mycosis fungoides, Sézary syndrome
			True histiocyte neoplasms
			Histiocytic medullary reticulosis
			Leukemic reticuloendotheliosis (some)
			Others (D)
			Unclassified neoplasms

Follicular center cell lymphoma, immunoblastic sarcoma, small lymphocyte lymphoma and plasmacytoid lymphocyte lymphoma are entities described by Lukes and Collins (see text). The comparison drawn by Lukes and Collins[36] between these neoplasms and the entities in the Rappaport system is indicated by letters in parentheses.

Lymphomas of Small and Plasmacytoid Lymphocytes

The small B lymphocytes of the cortical pulp and the medullary cords of normal lymph nodes synthesize surface Ig and, when stimulated by antigen, they transform rapidly to secretory plasma cells. Their surface receptors for C3 react weakly by comparison to the B cells at the centers of the follicles.[7,30] The similarity observed in the surface properties of the B cells in the medullary cords and of the tumor cells in *chronic lymphocytic leukemia*, *well-differentiated lymphosarcoma*, and *Waldenström's macroglobulinemia* suggested to Braylan et al.[7] that the three neoplasms may derive from the small lymphocytes and plasmacytoid lymphocytes that reside normally in the medullary cords of the lymph nodes and in corresponding B cell areas of the spleen and bone marrow. The neoplastic proliferation in each of these instances seems to originate from a single cell, judging from the monoclonal nature of the surface Ig. Each disease may be associated with a serum M protein and with immunodeficiency because of low levels of normal Ig's. The course of the diseases is highly variable and often rather indolent; elderly patients frequently die of unrelated causes. The life expectancy after diagnosis is usually 3 to 5 years. Survival in patients with the more aggressive forms of these diseases depends largely on (1) the size of the accumulated tumor cell load, (2) the degree of suppression of bone marrow function and immune competence, and (3) the occurrence of complications related to elaborated paraproteins (e.g., hyperviscosity) or autoantibodies (e.g., hemolytic anemia, thrombocytopenia). Although therapy with an alkylating agent and prednisone is partially successful in reducing the number of tumor cells and in ameliorating the hematopoietic and serologic complications, treatment may further impair immune competence. Many patients ultimately become refractory to therapy and succumb to uncontrolled infection.

Hodgkin's Disease

The hypothesis of Order and Hellman[42] as modified by Lukes and Collins[36] suggests that defective T cell surveillance permits the polyploid immunoblasts (Reed-Sternberg cells) and their abnormal mononuclear counterparts which develop in the course of viral infection to persist, eventually increase in number, disseminate, and produce clinical disease. Studies of thymidine incorporation by cells recovered from lymph nodes in Hodgkin's disease and an analysis of their nuclear DNA content are consistent with the existence of an aneuploid tumor cell line and a marked reactive process mounted by host lymphoid tissues.[43]

Differences are apparent in the clinical manifestations and in the histopathology of Hodgkin's disease as it occurs in younger and older patients.[32,38,41] The disease in younger patients is typically localized and asymptomatic. Few Reed-Sternberg cells are present in the involved lymph nodes and the host's lymphocyte and/or benign histiocyte reaction is vigorous (lymphocyte predominance and nodular sclerosis histologic types). The median survival after extended radiotherapy may be as high as 10 to 15 years and cures may be achieved.[48] In older patients, on the other hand, the disease is more likely to be widespread at presentation and it is often associated with systemic symptoms and with deficiency in delayed hypersensitivity. Although many Reed-Sternberg and/or malignant-appearing mononuclear cells are typically found, the host's lymphocyte reaction is restrained (mixed cellularity histologic type) or even sparse (lymphocyte depletion histologic type). Aggressive chemotherapy and radiotherapy may not be well tolerated and survival may be as short as 1 to 4 years or less.

The survival of patients with advanced stages of Hodgkin's disease (III and IV) can be prolonged by cyclic induction therapy with four drugs [nitrogen mustard or 1-(2 chloroethyl) -3 cyclohexyl-1 nitrosourea combined with a vinca alkaloid, procarbazine, and prednisone] followed by maintenance therapy with vinblastine and periodic courses of the four inducer drugs.[11,39] The potential usefulness of combined radiotherapy, chemotherapy, and immunotherapy in the treatment of advanced Hodgkin's disease is currently under investigation.[49,58]

Plasma Cell Neoplasms

Neoplastic proliferations of plasma cells are often detected by the recovery from plasma or urine of monoclonal immunoglobulin and/or light chains (M proteins) secreted by the tumor cells. Whereas some 20 gm of tumor (2×10^{10} cells) suffice to produce an electrophoretic M protein "spike" in the serum, the malignant nature of the neoplasm does not usually become apparent until the tumor growth reaches 200 to 500 gm. Death from multiple myeloma is likely once the tumor mass doubles three or four times to reach 4 to 10 kg; the doubling time during the clinical stage of the disease averages 4 to 6 months.[51]

The body burden of multiple myeloma cells can be reliably inferred from certain clinical correlates: severity of the anemia, level of the serum M protein, and the presence or absence of hypercalcemia and of lytic lesions of bone.[15] In a recent retrospective analysis of 482 myeloma patients treated with intermittent courses of melphalan-prednisone,[3] the major determinants of survival were (1) the pretreatment tumor cell burden and renal function and (2) the response to therapy. Median survival of patients with high initial tumor mass (>1.2 kg plasma cells/m^2 body surface) was 17 months, compared to 27 months in patients with intermediate tumor mass and 39 months in patients with low tumor mass (<0.6 kg plasma cells/m^2 body surface). The differential survival was not attributable to differences in the *frequency* of remission. About half the patients in each category of tumor mass improved clinically and achieved a 75 per cent or greater reduction in production of M protein. (Such responses were associated with a 1 to 2 log reduction in tumor cell number which thereafter reached a plateau phase.[51]) Rather, the median survival correlated with the *duration* of the remission which preceded the eventual relapse of a resistant cell population. Remissions were short in patients who had a high pretreatment tumor cell burden and in patients who maintained a relatively high plateau of residual tumor during therapy. Paradoxically, patients who achieved maximum tumor reduction rapidly (i.e., within two months) had shorter remissions and survival than patients with slower onsets of remission. This unusual course in the rapidly responding patients may have reflected sensitivity to chemotherapy of tumors with relatively high growth fractions and earlier emergence of resistant cell clones. Death from myeloma was most often due to infection or renal failure.

Precautions taken to avoid certain complications of myeloma, and measures aimed at reversing recently established complications can improve the quality and the duration of life. Ingestion of three quarts of liquid each day will facilitate the excretion of Bence-Jones protein, calcium, and uric acid and will reduce the risk of renal failure. The occurrence of acute hypercalcemia requires more vigorous hydration, as well as the administration of hydrocortisone, specific antimyeloma treatment, and, when necessary, oral or intravenous phosphate. The early institution of a program of ambulation, graded physical activity and oral analgesic therapy is a safe and effective way to relieve bone pain and to prevent collapse of vertebrae and compression of the spinal cord. If necessary for the palliation of pain, a limited dose of radiotherapy administered to localized skeletal areas is permissible, but extensive radiotherapy should be avoided as it further impairs the marrow reserve. The advent of frank compression of the spinal cord or cauda equina must be treated promptly with laminectomy followed by local radiotherapy. The bleeding, central nervous system symptoms, and the failure of the heart and the kidneys associated with serum hyperviscosity are often dramatically reversed by plasmapheresis. The onset of fever should trigger a search for a focus of infection; antibiotics are started immediately after the cultures are drawn. The administration of vaccines containing live virus should be avoided in patients with multiple myeloma as in immunodeficient or immunosuppressed patients generally.

In some individuals, proliferation of plasma cells apparently reaches a growth plateau at a subclinical level. Observation over a period of years reveals no change in the mild degree of marrow plasmacytosis and in the low level of serum M protein. The function of the bone marrow and the kidneys and the integrity of the immune and skeletal systems remain uncompromised. There is no evidence of extramedullary tumor growth and there are no complications attributable to M proteins (e.g., hyperviscosity, cryopathies, amyloidosis). The apparently benign monoclonal proliferation and gammopathy in these patients rarely undergoes malignant transformation after 5 to 20 years. No specific therapy is required or indicated unless this metamorphosis occurs. Benign plasma cell proliferations account for the bulk of the serum M proteins detected in 3 per cent of patients over the age of 70 years.[23]

MYELOID NEOPLASMS

The well defined myeloid neoplasms include polycythemia vera, myelofibrosis and myeloid metaplasia, essential thrombocythemia, chronic myelocytic leukemia, and acute myelocytic leukemia. Chronic myelocytic leukemia will not be discussed. Although it may occur at any age, chronic myelocytic leukemia is most common in patients between 30 and 50 years. Idiopathic thrombocythemia has been considered in connection with hemostatic disorders of the elderly.

Polycythemia Vera

Autonomous proliferation of a primordial stem cell present in the bone marrow and in embryonal sites of blood formation has long been regarded as the basic defect in polycythemia vera. According to this hypothesis, the hyperplastic primordial cell is precommited to differentiation into hematopoietic cells (erythoblasts, megakaryocytes, and granulocytes) and stromal cells (reticulum cells, fibroblasts, and osteoblasts). The clinical picture at various stages of disease reflects a changing balance in the proportions of the variegated proliferation and in the sites at which it occurs. The traditional ideas concerning the pathogenesis of polycythemia vera may require modification in view of recent evidence which suggests humoral regulation of the disturbed hematopoiesis in this disease.[60]

The erythrocytosis phase of polycythemia vera usually lasts 5 to 25 years. It is characterized by expansion of the red marrow at the expense of the fatty marrow and an absolute increase in the circulating red cell mass. Variable increase occurs in granulocyte production, platelet production, and the size of the spleen. With the passage of time, blood formation gradually shifts from its primary location in the marrow to extraosseous sites in the spleen and liver. This shift is accompanied by increasing fibrosis and osteosclerosis of the bone marrow, progressive enlargement of the spleen and liver, and the appearance of anemia and of abnormalities in the morphology and maturity of peripheral blood cells, e.g., tear-drop poikilocytes, agranular and giant platelets, young granulocytes, and nucleated red blood cells (leukoerythroblastosis). After several years in this "spent" or anemic phase, patients often die from debility and from complications, such as sepsis, heart failure, or hemorrhage. As many as 15 per cent of patients succumb to acute myelocytic leukemia which develops abruptly and represents both the natural evolution of polycythemia vera and the leukemogenic potential of the agents used to suppress it.

The survival of patients with polycythemia vera who are treated with ^{32}P is inversely related to age at the onset of the disease. The usual age at diagnosis is between 50 and 60 years, and the survival of those patients treated with ^{32}P varies on the average from 14 to 11 years. Such limited information as is available suggests that survival of patients treated with phlebotomy alone or with chemotherapy is shorter than that of patients treated with ^{32}P.[34]

The diagnosis of polycythemia vera is made readily when the findings include pancytosis and splenomegaly. When the initial clinical picture is that of erythrocytosis alone, relative polycythemia as well as secondary forms of true polycythemia must be considered. Relative (spurious, stress) polycythemia, the most frequent cause for a persistent elevation of the venous hematocrit, is characterized by a normal red cell mass and a normal or low plasma volume. The sina qua non for the diagnosis of true polycythemia, on the other hand, is an increase in the red cell mass to values in excess of about 36 ml per kg in men and 32 mg per kg in women. Relatively common causes of the secondary polycythemia encountered in patients of advanced age include (1) cardiopulmonary disease resulting in arterial oxygen saturation below 92 per cent and oxygen tension below 65 mm Hg, (2) an increased level of carbon monoxide hemoglobin in the blood of smokers which decreases arterial oxygen carrying capacity and increases the affinity for oxygen of the functional hemes, and (3) renal hypoxia due to cysts, hydronephrosis and, occasionally, renal artery stenosis. Mention should also be made of the rare occurrence of tumors which autonomously secrete erythropoietin-like materials (e.g., hepatoma, hydronephrosis, pheochromocytoma). If no secondary cause for the isolated erythrocytosis can be found and if the erythropoietin level in the serum is low, polycythemia vera may be diagnosed presumptively. Ancillary findings which tend to confirm this diagnosis include increased activity of leukocyte alkaline phosphatase and increased serum vitamin B_{12} and unbound B_{12} binding capacity.

The primary objectives of treatment in the erythrocytosis phase are to reduce the red cell mass with its attendant symptoms and hazards (of bleeding and thrombosis), to maintain the red cell mass and blood viscosity in the normal range, and to control any associated thrombocytosis. The first two objectives are initially achieved by the removal of red cells and the depletion of iron stores through venesection. If necessary because of thrombocytosis or frequent phlebotomy, venesection is supplemented by suppression of the marrow with ^{32}P or an alkylating agent. Because of the risks of acute gout and uric acid nephropathy, the prophylactic administration of allopurinol is indicated until suppression of the marrow is achieved. Elective surgery should be postponed until after hematologic control has been maintained for 4 or more months. Cyproheptadine (Periactin) may help to ameliorate the troublesome pruritus and dyspepsia attributable to hyperhistaminemia. Management of the "spent" or anemic phase will be discussed in the next section.

Idiopathic Myelofibrosis and Myeloid Metaplasia

Idiopathic myelofibrosis and myeloid metaplasia is a slowly progressive myeloproliferative process akin to polycythemia vera that begins as a panmyelosis which is not predominantly erythroid. In its fully developed form, it resembles post-polycythemia myelofibrosis and myeloid metaplasia. However, it may present a confusing clinical picture if diagnosed early in the course or when proliferation of the stromal elements remains modest. Thus myelofibrosis and myeloid metaplasia and chronic myelocytic leukemia of the Philadelphia chromosome–negative type may share several features in common such as clinical presentation at an advanced age, leukocytosis, anemia, thrombocytopenia, immature granulocytes in the blood, hyperplasia of granulocytes and megakaryocytes in the bone marrow, minimal myelofibrosis, and mild splenomegaly.

Myelofibrosis and myeloid metaplasia is usually diagnosed late in the course at an age of about 60 years; the average survival from the time of diagnosis is about 3 years. There is often a history of refractory anemia which has progressed insidiously and may now require blood transfusion. The anemia is multifactorial in origin; it results from reduced red cell production in the fibrotic marrow, ineffective erythropoiesis, and sequestration and premature destruction of defective erythrocytes in the enlarged spleen. The spleen may become massive in size, owing mainly to ectopic blood formation and overgrowth of fibrous tissue and reticulum cells. The course and outcome of myelofibrosis and myeloid metaplasia and of "spent" polycythemia vera are similar.

The debilitated condition of the patients, the tenuous nature of the residual blood formation, and the potentially serious side effects of the available treatment modalities require that therapy be undertaken with great caution. Androgens may be given to stimulate erythropoiesis, and prednisone to reduce splenic sequestration in patients who require frequent transfusions of packed red cells. The transfusion of platelets can improve hemostasis whether bleeding is attributable to platelet dysfunction or depletion. Small doses of irradiation directed at the spleen or cautious administration of busulfan may temporarily relieve the pressure symptoms and pain associated with massive splenic enlargement. Although the spleen is sometimes excised successfully in carefully evaluated patients with severe hemolytic anemia or life-threatening thrombopenia, the postoperative morbidity and mortality are high and the therapeutic benefit is often temporary.

Acute Myelocytic Leukemia

Acute myelocytic leukemia and its morphologic variants (promyelocytic, monocytic, myelomonocytic, erythroleukemia) constitute the predominant form of leukemia in adults; incidence increases with age. The vast majority of cases arise de novo. However, in some instances acute myelocytic leukemia follows refractory or aplastic anemia, or exposure to radiation or to leukemogenic chemicals; acute myelocytic leukemia has also constituted the terminal stage of hematologic malignancies (chronic myelocytic leukemia, polycythemia vera, myelofibrosis and myeloid metaplasia, multiple myeloma, or Hodgkin's disease) in patients treated previously with ionizing radiation and/or chemotherapy. The etiology of acute myelocytic leukemia is not known. The demonstration in acute myelocytic leukemia cells of RNA and RNA-directed DNA polymerase related in function and structure to similar materials in oncogenic viruses provides support for the hypothesis that RNA viruses may have an etiologic role in human leukemia as in leukemia of other species.[19]

The achievement of remission in acute myelocytic leukemia requires the production of bone marrow hypoplasia. Older patients and patients whose cellular immune responses are impaired before the institution of specific therapy are particularly vulnerable to death from sepsis during this period. One of the most effective treatment regimens for acute myelocytic leukemia is designed to induce hypoplasia of the marrow rapidly in the belief that the vulnerable periods of immunosuppression and of cytopenia will be shortened thereby. The regimen combines arabinosyl cytosine (Cytosar), given by continuous infusion for a period of 7 days, and bolus infusion of daunorubicin given during the first 3 days; a second, shorter course is given if a remission is not achieved. The preliminary data indicate that approximately half the patients over the age of 60 respond to this treatment with complete or partial remissions and begin the maintenance therapy; the median duration of survival in all treated patients over the age of 60 is about 7 months.[45] (The median survival of patients with acute myelocytic leukemia who are not treated is only 2 to 3 months). Additional improvement in survival awaits the development of effective methods for stimulation of immune competence and improved regimens for antibiosis and for the eradication of leukemia cells, particularly in sanctuaries not penetrated readily by antileukemia drugs (e.g., brain, meninges, gonads).

The major supportive efforts in the management of acute myelocytic leukemia include (1) the transfusion of platelets to prevent bleeding, red cells to correct anemia, and granulocytes to treat infection, (2) the careful investigation of fever and prompt institution of appropriate antimicrobial therapy, (3) the prevention of uric acid nephropathy by adequate hydration and the use of allopurinol. The liberal use of platelet transfusions has reduced the mortality from bleeding. Sepsis, rather than hemorrhage, has now become the leading cause of death. Pseudomonas, other gram-negative bacteria, and staphylococci constitute the major bacterial pathogens. The usual portals for entry of bacteria are the lungs, ulcers in the gastrointestinal and genitourinary tracts, rectal fissures, and breaks in the skin. Fungi, particularly candida and aspergillus, overgrow normal flora in the gastrointestinal and respiratory tracts of neutropenic patients treated with widespectrum antibiotics; dissemination of candida is assisted by infrequent rotation of intravenous catheters and needles.

Although the prognosis of acute myelocytic leukemia is generally improved by aggressive chemotherapy, there is at present no treatment approach that is uniformly applicable. Supportive measures alone may be the most appropriate for the patient who is debilitated by age or prior disease. The same is true for the occasional older patient whose leukemia smolders or progresses very slowly. Aggressive chemotherapy of acute myelocytic leukemia is best undertaken in settings which provide intensive nursing and physician care as well as sophisticated transfusion and laboratory services. All of these will be required to vigorously treat the frequent complications.

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Blood Bank
Coney Island Hospital
2601 Ocean Parkway
Brooklyn, New York 11235

Disorders of Hemostasis and Thrombosis in the Aged

*Shafkat Hussain, M.D.**

Hemostasis in elderly subjects can be affected by age-related physiologic changes in blood vessels, platelets, and the coagulation-fibrinolysis system, as well as by various clinical disorders and iatrogenic complications. Disorders of hemostasis can lead to a bleeding tendency, thrombus formation, or both.

Advancing years are associated clinically with an increased incidence of thrombosis and atherosclerosis. There are, however, few studies detailing age-related changes in the blood coagulation system. Todd et al.[24] found no difference in coagulation factors and platelet levels between normal subjects 50 to 80 years of age and younger people. In another study,[9] the most consistent findings were higher levels of factors XII, XI, and antithrombin III in elderly women than in elderly men and rises in factors XII, XI, X, XIII, V, and antithrombin in women reaching the seventh and eighth decades with a subsequent decline in those factors in extreme old age. Fagerhol and Abilgaard[6] described a gradual decline in antithrombin III levels in men from ages 18 to 66 and an age-related increase of antithrombin III in postmenopausal women. There has also been some controversy concerning the effects of sex and advancing years on factor VIII concentration. An increasing level of factor VIII concentration was found with advancing age until the sixth decade in two studies, but not found in a third study.

The clinical significance of the above physiologic changes is not clear. The discussion will now proceed to disorders of hemostasis frequently seen in elderly subjects.

VASCULAR PURPURA

In the following disorders, the major cause of bleeding or purpura is presumed to be an abnormality of the vessels or their supporting tissues. Platelets, platelet functions, and the coagulation system are normal in this group of disorders. The diagnosis is made from the appearance of the lesions and associated clinical findings.

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*Associate Chief of Hematology Division, Coney Island Hospital; Assistant Professor of Medicine, State University of New York, Downstate Medical Center, Brooklyn

SENILE PURPURA. This is a chronic disorder of the elderly characterized by ecchymotic spots of the extensor surfaces and radial borders of the forearm and the backs of the hands and neck. These spots arise spontaneously or as a result of trivial trauma, resorb slowly, and frequently leave an area of brown discoloration. The basic defect is one of degeneration and loss of dermal collagen. The distribution of the lesions corresponds to regions regularly exposed to sunlight. Similar lesions are seen in patients treated with adrenal corticosteroids and in patients with Cushing's syndrome.

DRUG-INDUCED VASCULAR PURPURA. A multiplicity of drugs such as dilantin, penicillin, and coumarin derivatives frequently present with extensive skin bleeding. Although quite alarming to the patient, such drug-induced vascular purpura usually subsides promptly when the use of the drug is discontinued. This disorder must be distinguished from thrombocytopenic purpura which may also be drug-induced and is of much greater clinical consequence.

PURPURA ASSOCIATED WITH INFECTIONS. Viral and rickettsial diseases, meningococcemia, subacute bacterial endocarditis, and other infections may produce purpura by means of vascular damage. Vascular purpura in infections should be differentiated from purpura which is caused by thrombocytopenia and/or disseminated intravascular coagulation (DIC).

HEREDITARY HEMORRHAGIC TELANGIECTASIA

This condition, also known as Osler-Rendu-Weber syndrome, is inherited as an autosomal dominant trait. Widespread telangiectatic lesions of skin and mucous membrane are found. The patients' complaints are related to recurrent hemorrhages and iron deficiency anemia. In elderly patients, hepatosplenomegaly is often associated. The enlarged liver is due to both telangiectatic lesions and post-necrotic cirrhosis resulting from transfusion-induced hepatitis. Pulmonary arteriovenous fistulae are found with increasing frequency with advancing age, more than 90 per cent of patients over age 60 being affected in one series.[13] These pulmonary lesions are usually multiple and may lead to hemoptysis, recurrent pulmonary infections and high output heart failure. Cyanosis, clubbing, polcythemia, and arterial aneurysms are also seen. The telangiectasias in elderly patients must be differentiated from purpuric lesions, spider nevi of liver disease, senile cherry angiomas, venous lakes, and venous stars. Diagnosis of pulmonary arteriovenous fistulae requires fluoroscopy and pulmonary angiography. In symptomatic patients, resection of these lesions in the lung is the definitive treatment.

DISORDERS WITH THROMBOCYTOSIS

Thrombocytosis in elderly subjects may be seen as part of the myeloproliferative disorders; secondary to acute or chronic infections, chronic inflammatory disease, or malignancy; as a reaction to chronic blood loss or hemolysis; after splenectomy; and in patients recovering from megaloblastic anemia with vitamin B_{12} or folic acid therapy. The platelet count elevation in secondary thrombocytosis is usually modest (400,000 to 600,000 per m^3), and it is clinically significant only as a harbinger of an underlying disorder. Occasionally, significant thrombocytosis is the first manifestation of occult malignancy.

Polycythemia Vera

Sustained thrombocytosis is most frequently seen in polycythemia vera. The latter is a disease of middle and later years of life, peak age of onset being between 50 and 60 years. Both thrombosis and hemorrhage are frequent complications in this disorder, occurring in 33 to 50 per cent of patients. Peripheral vascular manifestations such as cyanosis and erythromelalgia are seen in about 34 to 44 per cent of patients with polycythemia vera. Upper gastrointestinal hemorrhage is frequent and may be the first manifestation of disease. Thrombosis and hemorrhage during and following surgery occur in more than 75 per cent of patients with uncontrolled polycythemia vera. These complications result from hyperviscosity owing to increased red cell mass and possibly from increased platelet count and frequent qualitative platelet dysfunction.[2] The hyperviscosity results in impairment of blood flow, vascular distention and stasis.

Prudent therapy consists of periodic phlebotomy to maintain the hematocrit near normal. If the platelet count is near one million per mm^3 or if it rises toward this level during repeated phlebotomy, it is advisable to institute myelosuppressive therapy with an agent such as busulfan or melphalan, even though these agents may increase the risk of development of acute leukemia. The use of antiplatelet drugs (e.g., aspirin and dipyridamole) in patients with thrombocytosis and acute ischemia due to vascular occlusions has not been explored, but they may be of value along with myelosuppressive therapy.

Essential Thrombocythemia

Essential thrombocythemia is a myeloproliferative disorder with platelet counts persistently over 1 million per mm^3 in the presence of a normal red cell mass. This condition is seen mostly in patients over the age of 40. The mean age in our series of 8 patients was 69 years. Hemorrhage, especially from the gastrointestinal tract, has predominated in most clinical reports, and significant thrombosis has not been emphasized. However, in our experience with elderly patients, 6 presented with arterial thrombosis, five having incipient gangrene of the toes.

The peripheral smear in this condition shows giant platelets, and bone marrow aspirate reveals megakaryocytic hyperplasia. In vitro platelet function studies have shown absent epinephrine-induced, decreased ADP-induced, and normal collagen-induced platelet aggregation.[22] Enhanced spontaneous aggregation has also been seen. Results of therapy with busulfan have been excellent, and no maintenance therapy is generally required once the platelet count is normalized. If the patient presents with a serious, life-threatening thrombotic event (e.g., cerebrovascular thrombosis), platelet-pheresis and intravenous nitrogen mustard can reduce the platelet count more rapidly. Antiplatelet drugs (e.g., aspirin) have been used in this condition mainly for the relief of peripheral vascular symptoms in patients who had spontaneous in vitro platelet aggregation.[18]

Myelofibrosis with Myeloid Metaplasia

In myelofibrosis with myeloid metaplasia, a condition seen predominantly in the elderly, thrombocytosis occurs in about a third of the cases, especially in the earlier stages. Giant platelets and platelet function abnormalities have been also described in this condition. Platelet sequestration in a very large spleen lowers the platelet count in the later stages of the disease. Bleeding, most often manifested by easy bruisability or skin petechiae, occurs in a few patients.

THROMBOCYTOPENIC DISORDERS

Thrombocytopenia is a common hematologic problem in elderly patients. In a survey reported by Bottiger et al.[4] 54 per cent of patients with thrombocytopenia were over 50 years of age and 25 percent over 70 years of age. A list of the causes of thrombocytopenia in elderly patients is given in Table 1. In some patients, more than one mechanism for thrombocytopenia is present. For example, decreased synthesis of platelets because of myelophthisis, antibody-induced destruction, and an enlarged spleen all may contribute to the thrombocytopenia of a patient with lymphoma. Discussion of all the causes of thrombocytopenia is clearly beyond the scope of this paper. Emphasis here will be on those factors of major significance in the aged.

In the survey of Bottiger et al.[4] 18 percent of cases of thrombocytopenia were drug-related, and in the drug-induced thrombocytopenia group, 77 percent of the patients were above 50 years of age. Drugs can cause thrombocytopenia by immunologic or toxic platelet destruction, induction of generalized bone marrow aplasia or hypoplasia, or by selective megakaryocytic suppression. Chemotherapeutic agents such as 6-mercaptopurine, methotrexate, and cyclophosphamide, used for treatment of malignancy or as immunosuppressive therapy, regularly produce generalized suppression of the bone marrow. On the other hand, many drugs such as chloramphenicol, gold, and phenylbutazone, produce bone marrow aplasia and thrombocytopenia only in occasional cases.

Selective megakaryocytic suppression causing thrombocytopenia is induced by chlorothiazide, and the same drug may also induce immune destruction of the platelets. Mild asymptomatic thrombocytopenia occurs in as many as 25 percent of patients taking chlorothiazide, and perhaps more frequently in the elderly and in patients with congestive heart failure. Recovery from chlorothiazide-induced thrombocytopenia after discontinuation of the drug is very slow, and readministration of the

Table 1. *Selected Causes of Thrombocytopenia in Elderly Patients*

DEFICIENT THROMBOPOIESIS (DECREASED MEGAKARYOCTES)

- Generalized bone marrow suppression
  - Chemical agents: benzol and derivatives, related agents
  - Radiation
  - Chemotherapeutic agents: nitrogen mustard, 6-mercaptopurine, methotrexate
  - Drugs occasionally producing bone marrow suppression: chloramphenicol, gold, mesantoin, phenylbutazone
  - Idiopathic aplastic anemia
  - Aplastic anemia associated with viral hepatitis

- Generalized bone marrow infiltration
  - Metastatic carcinoma
  - Lymphoma
  - Leukemia
  - Plasma cell dyscrasia
  - Myelofibrosis
  - Gaucher's disease

- Selective megakaryocyte suppression
  - Chlorthiazide
  - Estrogen
  - Tolbutamide
  - Alcohol

- Ineffective thrombopoiesis
  - Megaloblastic anemia due to folic acid or vitamin B_{12} deficiency
  - Paroxysmal nocturnal hemoglobinuria
  - DiGuglielmo Syndrome (erythroleukemia) and other preleukemic syndromes

EXCESSIVE DESTRUCTION OR POOLING OF PLATELETS (NORMAL OR INCREASED MEGAKARYOCYTES)

- Immunologic destruction
  - Drug-induced platelet antibodies: e.g., by gold, chlorthiazide, quinine, quinidine, sulfa drugs
  - Autoantibodies in lymphoma, systemic lupus erythematosus
  - Idiopathic autoantibody (chronic ITP)
  - Isoimmune antibodies in post-transfusion thrombocytopenia
  - Other immunologic processes: e.g., allergies, anaphylactic reaction, immune complexes

- Non-immunologic destruction
  - Diffuse intravascular coagulation
  - Localized intravascular coagulation—aortic aneurysm
    - Microangiopathic hemolytic anemia associated with malignancy, uremia, malignant hypertension, prosthetic cardiac valves
  - Septicemia (bacterial, viral, or rickettsial)
  - Massive transfusion of a bleeding patient with bank blood (dilution)

- Abnormal platelet pooling in large spleen due to:
  - Portal hypertension
  - Myeloproliferative disorders
  - Lymphoma
  - Paraproteinemia
  - Gaucher's disease
  - Feltys syndrome

drug for protracted periods is usually required to reproduce thrombocytopenia. Alcoholism and tolbutamide are also causes of thrombocytopenia by megakaryocytic suppression.

A few drugs, particularly quinine, quinidine, gold, digitoxin, and sulfa derivatives have been shown to cause thrombocytopenia by producing antibodies or complexes of antibody, drug and complement which damage platelets. Antibodies damaging platelets can be detected by several methods, but a test involving platelet factor III availability after immune injury to normal platelets in the presence of the patient's serum and the offending drug is most sensitive.[14] In contrast to thiazide-induced thrombocytopenia, which is insidious, patients with quinidine toxicity usually present with bleeding of acute onset and severe thrombocytopenia. Withdrawal of the offending drug is the only treatment usually required in drug-related thrombocytopenia and recovery is usually complete in one week. In patients with unexplained thrombocytopenia, discontinuation of all drugs that a patient is receiving should be considered.

Megaloblastic anemia of vitamin B_{12} deficiency (due to pernicious anemia) or folic acid deficiency (due to poor nutritional intake) can cause thrombocytopenia because of ineffective thrombopoiesis. Although seldom severe and rarely of clinical significance, it has occasionally led to purpura. Giant platelets with abnormal platelet function and prolonged bleeding time (out of proportion to the degree of thrombocytopenia) have been described. Treatment of megaloblastic anemia may lead to transient thrombocytosis with sticky platelets and occasional thrombosis.

In the past, idiopathic thrombocytopenic purpura (ITP) has been considered relatively rare in elderly people, but in a series of cases of ITP reported by Aster et al.,[1] the median age of the patients was 65. ITP should always be a diagnosis of exclusion. In addition to checking the patient's drug history, an antinuclear antibody test should be performed to rule out a collagen disease before ITP is diagnosed. A palpable spleen should also alert the clinician to other possible causes of thrombocytopenia. In contrast to children, ITP in adults is often chronic and recurrent. Aster et al.[1] found no significant differences in clinical features between young adults and elderly patients with ITP. However, age may be a factor in response to therapy in ITP. Harrington[11] observed a favorable response to splenectomy in ITP in 88 per cent of patients below the age of 45 as compared to a 59 per cent response rate in patients above the age of 45. This is perhaps explained by the finding of Najen et al.[16] that 48 per cent of patients with ITP over the age of 50 had predominantly or exclusively hepatic sequestration of platelets compared to 4 per cent of patients below the age of 15. A predominantly or exclusively splenic sequestration pattern was seen in 35 per cent of patients over the age of 50 as compared to 85 per cent of patients below the age of 15 years.[16]

Thrombocytopenia can occur in viral, rickettsial, and bacterial infection with or without disseminated intravascular coagulation. The mechanism in the absence of DIC has been attributed to platelet aggregation induced by endotoxin, antigen-antibody complexes, or offending organisms and to increased platelet consumption on the damaged walls of small blood vessels. Thrombocytopenia is a frequent finding in gram-negative sepsis, and the finding of unexplained thrombocytopenia in an elderly patient even without fever or leukocytosis should arouse suspicion of sepsis.

QUALITATIVE PLATELET DEFECTS

Qualitative platelet defects in elderly patients are usually due to acquired clinical disorders or are drug-related (Table 2).

In patients with uremia, decreased platelet factor III availability, diminished ADP-induced, epinephrine-induced and collagen-induced platelet aggregation, and prolonged Ivy bleeding time are often associated with clinical bleeding (petechiae, bruises, epistaxis and bleeding from the gastrointestinal tract). The platelet abnormalities have been attributed to increased plasma concentration of guanidino-succinic acid, phenol, and phenolic acid. These platelet defects are corrected by dialysis (particularly peritoneal dialysis), and clinical bleeding as a result of platelet dysfunction in uremic patients is an indication for dialysis.

In liver disease, there are usually multiple abnormalities in platelets and the coagulation-fibrinolysis system. Platelet function abnormalities in liver disease consist of diminished platelet factor III availability and decreased ADP and collagen-induced platelet aggregation. This platelet dysfunction is attributed to coating of platelets by serum fibrinogen/fibrin degradation products.

A number of drugs frequently prescribed for elderly subjects affect platelet function (Table 2). Some, such as aspirin, dipyridamole, and clofibrate, are at present under clinical investigation for antithrombotic effect. These drugs lead to inhibition of platelet aggregation through impairment of release reaction, impaired ADP or epinephrine-induced platelet aggregation, or through an effect on cyclic AMP. Their role in causing clinical bleeding is not known, but they probably contribute to a bleeding tendency in patients with other hemostatic defects and may lead to an increase in bleeding during surgical procedures. Drugs causing platelet dysfunction should be discontinued in patients with other hemostatic defects 7 to 10 days prior to elective surgery.

VITAMIN K DEFICIENCY IN THE ELDERLY

Vitamin K is essential in the synthesis of coagulation factors II, VII, IX, and X in the liver. A deficiency of vitamin K, liver disease, or a competitive antagonist of vitamin K (coumarin derivatives) can lead to deficiency of these coagulation factors and clinical bleeding. Vitamin K1 is found in various foods, and vitamin K2 is synthesized by intestinal bacteria. Absorption of vitamin K, a fat-soluble vitamin, requires bile, and in patients with obstructive jaundice, a significant deficiency of vi-

Table 2. *Selected Causes of Platelet Dysfunction in Elderly Patients*

CLINICAL DISORDERS	DRUGS
Uremia Liver disease Myeloproliferative disease Paraproteinemia Acute leukemia Disseminated intravascular coagulation Pernicious anemia Systemic lupus erythematosus Alcoholism	1. Inhibitors of the platelet release reaction: e.g., aspirin, indomethacin, phenylbutazone, phenothiazine and antihistamines, tricyclic antidepressants, dextran, heparin, ethanol, clofibrate. 2. Inhibitors of platelet responsiveness to ADP: e.g., glyceryl guiacolate, dipyridamole. 3. Inhibitors of platelet responsiveness to epinephrine: e.g., dibenzylene, phentolamine, propranolol. 4. Agents which increase concentration of cyclic AMP: e.g., prostaglandin E, theophylline, papaverine, dipyridamole.

tamin K can occur. In a study from England[12] of 110 hospitalized patients between the ages of 56 and 100, a low thrombotest level was found in about 75 per cent of the cases, but in most cases it returned to normal with oral administration of vitamin K. This suggests a high incidence of vitamin K deficiency in the elderly in England. Some patients who continued to have low thrombotest levels were found to have liver disease. How frequent and clinically significant vitamin K deficiency is in elderly patients in this country is not known. In patients receiving prolonged antibiotic therapy, suffering from malabsorption syndrome, or about to receive anticoagulant therapy, a prothrombin time or thrombotest should be performed to check for possible vitamin K deficiency or liver disease.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

Bleeding diathesis and thrombotic complications in an elderly patient can be due to a syndrome of diffuse intravascular coagulation in acute, subacute, or chronic form. There is always a serious underlying pathologic process causing DIC (Table 3), which must be recognized and treated. These diverse conditions can cause activation of the clotting process through the intrinsic or extrinsic system. Thromboplastic substances from damaged or neoplastic tissues enter the circulation and lead to activation of the extrinsic system of clotting. In infections, damage of endothelium by endotoxin leads to exposure of collagen and activation of the Hageman factor. Endotoxin and antigen antibody complexes also induce platelet aggregation, and platelet factor III is made available to take part in the intrinsic system of clotting. Activation of clotting leads to thrombin formation, conversion of fibrinogen into fibrin, and intravascular deposition of fibrin. At the same time, activation of fibrinolysis through plasminogen activators released from the same tissue breakdown, particularly in the microcirculation, leads to fibrinolysis, a mechanism protecting against vessel occlusion. The breakdown products of fibrin form soluble complexes with fibrinogen and fibrin monomer and inhibit the thrombin-fibrinogen reaction, polymerization of fibrin, and aggregation of platelets.

These anticoagulant and antiplatelet effects, along with depletion of coagulation factors and platelets, are responsible for bleeding in DIC. The other clinical manifestations of DIC are thrombi in large and small vessels (e.g., thrombophlebitis, gangrene of fingers and toes, and strokes), shock, hemolysis and renal failure. DIC in elderly patients should be suspected in the setting of clinical conditions given in Table 3.

Laboratory confirmation is obtained by demonstrating increased serum levels of fibrin split products and the presence of fibrin monomer in plasma. The latter can be accomplished with the serial dilution protamine sulfate tests and other tests of paracoagulation. The concentration of platelets and of the clotting factors involved in DIC (K, II, V, VIII, and XIII) are variable and depend on the relative rates of consumption and compensatory synthesis. They may be high, normal or low.

The treatment of DIC consists of: (1) treating the underlying disease such as leukemia, infection, or heat stroke; (2) treating the precipitating event such as shock or acidosis; (3) replacing depleted blood components by transfusion of red blood cells, platelets, fresh frozen plasma, and cryoprecipitate if the patient is bleeding. The use of heparin in DIC is controversial, and the tendency at present is to avoid its use, although

Table 3. *Selected Causes of Disseminated Intravascular Coagulation in Elderly Patients*

- Infection
    - Viruses, e.g., disseminated herpes infection
    - Bacteria, e.g., gram-positive and gram-negative sepsis
    - Rickettsial, e.g., Rocky mountain spotted fever.
- Neoplasm
    - Carcinoma, leukemia (particularly acute promyelocytic leukemia)
- Surgical procedures
    - Prostatic surgery, lung surgery, extracorporeal circulation
- Extensive tissue damage
    - Trauma, burn, heat stroke, shock
- Antigen-antibody reactions
    - Drug reactions, hemolytic transfusion reaction, anaphylaxis
- Miscellaneous
    - Ruptured abdominal aortic aneurysm, dissecting aortic aneurysm, acute pancreatitis, liver disease

heparin is occasionally indicated in patients with thrombotic manifestations secondary to chronic DIC.

ABNORMALITIES OF HEMOSTASIS AND COAGULATION IN MALIGNANCY

Patients with cancer are prone to develop vascular thrombosis and hemorrhages. Sometimes vascular thrombosis is the initial manifestation of an otherwise unsuspected neoplasm.

Recurrent thrombophlebitis in carcinoma of the pancreas and hemorrhagic manifestations of acute promyelocytic leukemia are well known, but arterial, venous, and small vessel thromboembolic and hemorrhagic complications are also frequently seen in other malignancies. In a Mayo Clinic study of 61 patients (35 patients over the age of 60) with various malignancies, Sun et al.[23] noted recent or current bleeding in 56 per cent and thromboembolism in 20 per cent, in patients both with and without metastases. The majority of patients in this study had various abnormalities in hemostasis. Overall, the most frequent abnormalities were prolonged prothrombin and thrombin times, increased fibrinogen and serum fibrinogen/fibrin split products, and positive serum dilution protamine sulfate test. Yet in another study[15] in 50 patients with disseminated malignancy, the most common pattern was the "hypercoagulable state." This included short bleeding time, decreased silicone coagulation time, partial thromboplastin time, increased tolerance to heparin, and marked elevation of plasma levels of factors I, II, V, VIII, IX, and XI.

Thrombocytosis, usually 400,000 to 600,000 per mm^3, is commonly associated with all types of neoplasm and on occasion may be elevated to a marked degree (over 1 million per mm^3). The relationship of increased platelets and coagulation factors in malignancy to increased incidence of thromboembolic manifestations is not clear but appears to be close. Thrombocytopenia in malignancy may also occur for almost all the reasons given in Table 1.

COAGULOPATHY IN AORTIC ANEURYSM

Aneurysmal dilatation and dissection of the aorta have been associated with extensive coagulation disorders.[3,5] The coagulopathy consists of prolonged prothrombin time due to decrease of factors II, V, VII, or X, decreased levels of factor XII and XIII, significant elevation of serum fibrinogen and fibrin degradation products, and thrombocytopenia.[5] It probably reflects a localized consumption of clotting components triggered by exposed collagen and the release of thromboplastic material from the aortic wall. The coagulopathy of aortic aneurysms is rarely associated with a frank hemorrhagic diathesis. Nevertheless, the finding of abnormal clotting parameters may be of diagnostic value in differentiating dissecting aneurysm from a myocardial infarction. A clotting survey should be performed preoperatively in all patients undergoing surgery for arterial aneurysms.

ACQUIRED INHIBITORS OF COAGULATION FACTORS

Factor VIII Inhibitors. Factor VIII inhibitors have been reported[21] in elderly patients of both sexes with rheumatoid arthritis, systemic lupus erythematosus, temporal arteritis, various skin diseases including pemphigus, psoriasis, and dermatitis herpetiformis, and in at least 25 elderly patients without underlying disease. In several patients, including some patients with skin diseases, the inhibitor developed after penicillin therapy. In all cases in which it has been studied,[21] the inhibitor has had the characteristic of a monoclonal immunoglobulin and in a number of cases, it has been shown to be IgG.

A number of patients with factor VIII inhibitors have presented with severe bleeding syndromes and unmeasurable factor VIII levels. They had previously been free of bleeding tendency and had no family history of abnormal bleeding. In patients with skin diseases and factor VIII inhibitor, severe protracted courses have been noted.

Treatment of acute bleeding episodes in patients with inhibitors is generally similar to that of hemophiliacs with inhibitors (transfusion of concentrated factor VIII). Patients with collagen-vascular disorders and inhibitors have shown a good response to corticosteroids. Corticosteroid therapy alone has usually not resulted in remission in patients without underlying disease. In these patients, a combination of prednisone and other immunosuppressive drugs (6-mercaptopurine and cyclophosphamide) has been used with some success.

Inhibitors of Other Coagulation Factors. Of 11 patients with acquired inhibitor of factor V described in the literature,[21] 8 patients were over the age of 60. Five were men. All previously had an apparently normal hemostatic mechanism. Four patients had been receiving streptomycin, 6 developed the inhibitor postoperatively and 6 patients had systemic infection. In 7 patients with this inhibitor, there was a bleeding diathesis. In general, inhibitor titers were low, and improvement in hemostasis could be achieved by transfusion of factor V in fresh frozen plasma. The inhibitor was short-lived in the majority of patients.

Two patients over the age of 60, both men and both receiving isoniazid, have been described with acquired inhibitors of fibrin polymerization. Both patients had a severe bleeding diathesis. These inhibitors are believed to affect fibrin crosslinking.

HEMOSTATIC DEFECTS IN DYSPROTEINEMIAS

Both multiple myeloma and macroglobulinemia are primarily diseases of old age with peak incidences in the sixth and seventh decades. Bleeding is sometimes of major importance in both diseases (more often in macroglobulinemia), and various abnormalities in hemostasis have been described. In the series reported by Perkin et al.[17] patients with paraprotein containing kappa chain had a markedly increased tendency to bleed. Patients with IgA myeloma bled as often as patients with macroglobulinemia, and bleeding was less frequent in IgG myeloma. Various abnormalities in hemostasis include thrombocytopenia, platelet dysfunction (decreased platelet adhesiveness and decreased platelet factor III availability), prolonged bleeding time, prolonged prothrombin time and partial thromboplastin time, and decreased coagulation factors (factors VII, VIII, X and XI). Clots are sometimes abnormally pliable and lack many properties of normal clots such as spontaneous retractability (gelation phenomenon).

Abnormal platelet counts and thrombin time are more frequent in multiple myeloma than in macroglobulinemia.[17] In contrast, abnormal platelet adhesiveness and decreased coagulation factors are more often seen in macroglobulinemia and IgA myeloma than in IgG myeloma.[17] Abnormalities in platelet count and thrombin time are not highly correlated with clinical bleeding. Coagulation factors, although usually low in patients who bleed, have been rarely low enough to be a primary cause of bleeding. The most significant association between tests of hemostasis and abnormal bleeding are seen with tests related to platelet plug formation.[17] All patients in Perkin's series who bled had abnormal bleeding and/or platelet adhesiveness.[17] The bleeding was mostly in skin and mucosal surfaces. Incidence of bleeding is correlated directly with concentration of plasma protein.

Prolonged thrombin time is usually attributed to an inhibitor of the thrombin-fibrinogen reaction. Elevated levels of plasma protein can be correlated with abnormal values in thrombin time and prothrombin time. The gelation phenomenon has been demonstrated to be due to binding of fibrin monomer by abnormal immunoglobulin. When bleeding is a problem, control of hemostasis is achieved by plasmapheresis.

THE FIBRINOLYTIC SYSTEM

The fibrinolytic enzyme system is a potentially powerful biologic mechanism that can be activated to digest fibrin thrombi and lyse fibrinous exudates. The relevance of the fibrinolytic system to the development of atherosclerosis is still uncertain. Studies of fibrinolytic activity in various age groups have shown conflicting results. Hamilton et al.[8] found an increase in fibrinolytic activity in people over 75 and an increase in levels of alpha$_1$-antitrypsin and alpha$_2$-macroglobulin (inhibitors of plasmin) and plasma fibrinogen with aging. Plasma fibrinogen and plasminogen concentrations were lower in people over 85 years than those under 85 years.

Other investigators found fibrinolytic activity to be lower in older subjects than in younger age groups. Robertson et al.[19] compared fibrinolytic activity in blood taken from arms and legs in different age groups and found that there was more of a decrease in fibrinolytic activity in the legs than in the arms of older persons. They suggested that this may be related to an increased incidence of thrombosis in the legs of older subjects. Plasma fibrinolytic activity has also been found to be somewhat reduced in patients suffering from diseases which have a thrombotic component such as intermittent claudication, pulmonary embolism, deep vein thrombosis and myocardial infarction.

In older persons, disorders of fibrinolytic activity causing bleeding are usually secondary to disseminated intravascular coagulation and to fibrinolytic activator therapy (e.g., streptokinase, urokinase) for thromboembolic manifestations. Primary fibrinolysis is thought to be a rare disorder seen in patients with carcinoma, particularly carcinoma of the prostate.

DISORDERS PREDISPOSING TO OCCLUSION OF BLOOD VESSELS

The major factors in the pathophysiology of thrombosis—abnormalities of vessel wall, alterations of blood flow, and composition of blood (Virchow's triad)—have been recognized since the fifteenth century. The important role of platelets in arterial thrombosis has been corroborated by studies demonstrating their selective utilization and consumption.

Studies of platelet adhesion and platelet retention in patients with obesity, diabetes, hypertension, history of smoking, ischemic heart disease, stroke, and peripheral arterial disease have shown "sticky" platelets, but there have been inconsistencies both in the methods used and in the results obtained. There is also evidence in some patients that increased platelet "stickiness" is often the result rather than the cause of thromboembolic disease. Platelet aggregation studies using ADP, epinephrine, and collagen have shown hyperaggregability of platelets in patients with diabetes (clinical and latent), type II hyperlipidemia, ischemic heart disease, and diabetic retinopathy. Platelet kinetic studies have revealed a relationship between increased platelet turnover and increased thromboembolic risk in patients with cardiac prosthetic valves, rheumatic mitral valve disease, arterial and aortic prosthetic grafts, and after coronary artery bypass surgery.

The role of platelets in the pathogenesis of atherosclerosis is also under investigation. Harker et al.[10] showed selective increase in platelet consumption in patients with homocystinuria, an inborn error of metabolism characterized by increased frequency of atherosclerosis and thromboembolism. Dipyridamole reversed the increased platelet turnover in their patients. Employing a baboon model, these investigators produced experimental homocystinemia and found focal vascular deendothelialization with the appearance of circulating endothelial cells, increased platelet consumption and smooth muscle cell proliferation in the intima. Dipyridamole prevented this atherosclerotic-like process and decreased platelet consumption. In an in vitro study,[20] released material from platelet was shown to stimulate smooth muscle proliferation.

Platelets have also been recently implicated in initiating venous thrombi although stagnant blood flow and alterations in the composition of blood ("hypercoagulant state") are of greater importance.

Studies[24] of the blood coagulation system in elderly patients with diabetes mellitus and stroke revealed statistically significant differences from normal subjects, but their clinical significance is not clear. Of particular interest is the decrease in antithrombin III with age. Since a similar decrease has been noted in postoperative patients and in women taking oral contraceptive agents, deficiency of this factor may be etiologically related to the increased incidence of venous thrombosis in elderly people.

Other factors to be evaluated in patients with extensive or recurrent arterial venous or small vessel occlusive disease are listed in Table 4.

ANTIPLATELET DRUGS

Various antiplatelet drugs such as aspirin, sulfinpyrazone, dipyridamole, dextran, and clofibrate are at present undergoing extensive clinical trials in many thromboembolic conditions.[7] Sulfinpyrazone therapy has been reported to reduce the frequency of transient cerebral ischemic attacks and death from vascular causes in elderly patients with a history of prior stroke and myocardial infarction.[7] Dipyridamole has been effective in reducing the incidence of embolic episodes in patients with prosthetic heart valves.

There are several case reports in the literature on the benefit of aspirin in patients with thrombocytosis and painful, cyanotic fingers and

Table 4. *Some Factors Predisposing to Thrombosis*

- Abnormal fluid phase of blood
  - Paraprotein which increases viscosity of the serum: e.g., macroglobulinemia,
    - Circulating immune complexes which damage blood vessel linings: e.g., Sjogren Syndrome
  - Abnormal fibrinogen molecule: e.g., fibrinogen Baltimore; fibrinogen, New York
  - Chronic disseminated intravascular coagulation
  - Increased concentration of activated clotting factors: e.g., malignancy
  - Decreased concentration of antithrombin III: e.g., hereditary deficiency, old age
  - Impaired fibrinolysis: e.g., increased inhibitors of plasminogen activation

- Abnormal cellular phase of blood
  - Increased platelets and abnormal function: e.g., essential thrombocythemia
  - Increased red blood cell mass (increased viscosity): e.g., polycythemia vera

- Abnormal vessel wall
  - Athersclerosis
  - Endothelium damaged by inflammation, trauma, homocystinuria, or other causes.

- Stagnant blood flow
  - Immobility (bed rest), congestive heart failure
  - Incompetent venous valves (varicose veins)
  - Obstructed venous return: e.g., intra-abdominal malignancy compressing inferior vena cava

toes.[18] Retrospective data suggest that aspirin may have value in the prevention of myocardial infarction. It has not shown consistent benefit in prevention of venous thrombosis. More definitive information about the value of antiplatelet drugs in coronary artery and cerebrovascular disease will be provided by multicenter, prospective, controlled trials currently in progress in Canada and the United States.

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Coney Island Hospital
2601 Ocean Parkway
Brooklyn, New York 11235

Heat Stroke in the Elderly

*Mary Wheeler, M.D.**

Man, being a warm-blooded animal, normally maintains a constant body temperature in hot weather. If the mechanisms for temperature control are overwhelmed, body temperature may rise precipitously, resulting in heat stroke. Inadequate methods of temperature control caused by other diseases, or excessive heat production by the body are usually contributing factors. Epidemics of heat stroke occur among the elderly each year; during one heat wave more than 1000 people died in New York City. Heat stroke is important because of its high mortality rate (up to 50 per cent) even with optimal therapy, and because it is predictable and preventable by simple measures. This discussion will deal with the normal mechanisms for production, dissipation, and control of body heat, the pathophysiology of heat stroke and other disorders caused by heat, the clinical features of heat stroke, and the therapy and prevention of heat stroke.

PHYSIOLOGY OF TEMPERATURE CONTROL AND BODY COOLING

Under most circumstances, the body temperature exceeds the ambient temperature and heat is transferred out of the body. About two thirds of the body's normal heat losses occur through radiation and convection of heat; the rest of the heat is lost through insensible evaporation from the skin and lungs. Small amounts are also lost through the urine and feces, and variable, usually insignificant amounts may be lost by conduction. Conservation of body heat is achieved through basal metabolic heat production, by muscular work including involuntary shivering, and through peripheral vasoconstriction. In addition, higher brain centers promote behavior such as putting on heavy clothing, or going to a warmer place, which may help to conserve body heat.

As the ambient temperature approaches body temperature, loss of body heat through radiation and convection is sharply curtailed, and when environmental temperatures exceed 99°F, heat transfer is reversed. Under these conditions all heat losses must be achieved by evaporation.

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*Associate Chief, Endocrinology and Metabolism Division, Coney Island Hospital; Assistant Professor in Medicine, State University of New York, Downstate Medical Center, Brooklyn, New York

The main center for thermoregulation in the body is in the hypothalamus. Here local thermoreceptors sense the local temperature, which is a function of the supply of heated (or cooled) blood to the area. Autonomic impulses to increase body sweating and peripheral vasodilatation result from hypothalamic temperature elevations. Experiments on local heating and cooling of various parts of the body show that regional variation of sweating can be induced. These studies, and observations on patients with spinal cord transections who retain a limited capacity for heat-induced sweating, show that other sensory centers for temperature control exist, and that they probably are located at the spinal cord level.

Exposure to high temperatures has both immediate and delayed effects on body physiology. The immediate response is cutaneous vasodilatation with an increase in blood flow to the skin and an increase in sweat production. Cutaneous vasodilatation permits maximum losses through radiation and convection and supplies the metabolic needs for the production of sweat. With moderate heat exposure, the increased blood flow to the skin is achieved at the expense of flow to other organs. Greater stress increases the pulse rate and cardiac output. Flow to other organs also increases, and the fall in peripheral resistance is compensated for by an increase of up to 10 per cent in blood volume. These cardiovascular changes are accompanied by an increase in the respiratory rate. The blood volume expansion causes a relative decrease in the serum protein concentration. This decrease in serum proteins, along with the increased peripheral blood flow, probably accounts for the edema frequently seen at the onset of warm weather.

There are more than two million eccrine sweat glands in the body. Sweat production increases sharply with increasing temperature. Sweating of 2 to 8 liters per 24 hours is observed under conditions of heat exposure and moderate physical activity. Sweat is composed chiefly of sodium and chloride in water, and although the concentration varies widely, values in the range of 30 to 50 mEq per liter are often seen. It is estimated that an average person loses about 2 grams of NaCl in each liter of sweat at the beginning of warm weather. This loss of sodium is the basis for the common practice of ingesting salt tablets during hot weather. Sweating is an efficient means of cooling when the humidity is low, with up to 600 Kcal dissipated for each liter of sweat that evaporates. When the humidity rises, evaporation of sweat decreases. No heat loss results from sweat which drips off or remains in clothing.[8]

The means for delayed adaptation to heat are collectively known as acclimatization. Acclimatization, or the increased capacity to do work at high environmental temperatures, has been well studied because of its military implications. It has been consistently observed in military bases in the southern United States, and by the British in tropical climates, that new recruits were almost unable to work for the first few days. By the end of the first week, however, they were able to tolerate the high temperatures without becoming exhausted or collapsing as they did during their initial exposure to heat. Acclimatization involves modifications in neural or sensory, hormonal, and cardiovascular physiology, and the changes in cardiovascular physiology are very similar to those observed during general physical training. After acclimatization there is less subjective discomfort during heat exposure. There is also less of an increase in pulse and respiratory rates under the same conditions of heat stress, and greater cardiovascular stability with postural changes and with activity. Skin and rectal temperatures remain closer to normal, and changes in sweating occur. Sweat production after acclimatization is increased, with rates of 2 to 3 liters per hour reported. Sweating commences after a shorter exposure to heat and work, or at a lower environmental temperature than before acclimatization, and the concentration of sodium chloride is greatly reduced, to as low as 5 mEq per liter. These changes, as well as the previously described volume expansion, are mediated through enhanced secretion of aldosterone by the adrenal gland. The process of acclimatization is also characterized by a temporary decrease in urinary sodium excretion and a period of negative nitrogen balance. The sodium-conserving effects are reproduced by the administration of sodium-retaining steroids. If these steroids are given for several days and then discontinued, acclimatization is impeded or lost.

Full acclimatization can occur in 4 to 7 days, and as little as 90 minutes of exposure to heat per day will suffice. The degree of acclimatization achieved is enhanced by previous physical conditioning and by exercise. Once achieved, acclimatization is maintained for several weeks without re-exposure to heat, or for longer periods with brief re-exposures. The extent of acclimatization depends on the physical condition of the individual and the degree of heat exposure, and should not be thought of as an all-or-none phenomenon.[2]

DISORDERS CAUSED BY HEAT

Excluding dermatologic disorders such as prickly heat and sunburn, three distinct syndromes are associated with exposure to heat. Each results from a malfunction of rather specific mechanisms of heat adaptation. The most commonly seen syndrome, heat cramps, results from an excessive loss of sodium chloride from the body because of sweating. In these patients, thirst mechanisms are intact, blood volume is usually well preserved, and the individual is alert but complains of severe cramps and painful contractions of the muscles. This disorder is both treated and prevented by oral replacement of sodium chloride. As salt tablets may cause nausea, adding salt to the food is preferred. Heat cramps occur only in individuals who sweat profusely, and like all disorders due to heat, tend to occur at the beginning of warm weather before acclimatization. Under these conditions, sweat losses of sodium are relatively high. The elderly are seldom able or disposed to perform the degree of physical activity necessary to produce such large sweating losses over a period of time, and hence heat cramps are seldom seen in the elderly, even in individuals following sodium-restricted diets.

A second syndrome results from inadequate cardiovascular responsiveness to the circulatory changes induced by heat. The initial diversion of blood flow to the skin is not adequately compensated by vasoconstriction at other parts of the body, or by volume expansion. This disorder is known as heat exhaustion and is characterized by pallor, profuse sweating, vomiting, an urge to defecate, giddiness, and postural syncope. The similarity to the typical "vasovagal" attack should be noted. The condition is ordinarily relieved by lying down and resting; volume expansion with intravenous saline solution may enhance recovery but is usually unnecessary. This syndrome is frequently seen among the elderly who are at special risk because of a high incidence of cardiovascular disease, sluggish vascular autonomic responses, and frequent use of diuretic agents.

The third syndrome results from a relative or absolute failure of all mechanisms for body cooling to maintain body temperature, and severe hyperpyrexia ensues. This syndrome is known as heat stroke. Much of the literature on the subject describes the disorder in young, healthy individuals. Heat stroke in the young differs from heat stroke in the elderly since in younger individuals, it is almost always precipitated by heavy, usually compulsory physical exercise, generally under conditions of poor acclimatization. Examples include military recruits in basic training, high school or collegiate football trainees in the first days of fall practice, and miners, especially where confined conditions underground do not allow for the evaporation of sweat. The strenuous muscular work in which these subjects are engaged contributes to the development of heat stroke by enhancing production of body heat. The hyperpyrexia is associated with extensive muscle damage characterized by myoglobinuria, oliguria, and severe hyperkalemia. Myocarditis may also be seen in such patients. These complications are seldom seen in the elderly, where severe muscular work is not ordinarily a contributory factor to the development of heat stroke.

Some patients, after exposure to heat, have a clinical picture that includes elements of more than one of the above syndromes, and in such cases the treatment must be modified. Nonetheless, all of the disorders of heat are often seen in their "pure" form.

HEAT STROKE

Pathophysiology

Studies on sweating have shown that, under conditions of maximum heat stress, initially high rates of sweat production cannot be maintained indefinitely, and when the rate of sweat production falls, body temperature rises abruptly. This phenomenon is known as sweat fatigue and is felt to be an important factor in the pathogenesis of heat stroke. Sweat fatigue seems to be no more mysterious than fatigue of any sort, and is analogous to the ability of a sprinter to attain higher rates of speed than a marathon runner. Sweating may cease with sweat fatigue, but if cooling is effected by other means, it may be resumed after a period of rest. Some feel that hyperpyrexia per se can inhibit sweating, but certainly the absence of sweating for whatever cause only serves to intensify the hyperpyrexia.

Before heat stroke occurs, the ambient temperature is usually over 95°F. In most reported epidemics, more than 48 hours of temperatures averaging over 90°F were recorded, and relative humidity was in the range of 50 to 75 per cent. Epidemics of heat stroke, then, can be predicted with a high degree of accuracy.

Cardiovascular disease is the single most important factor predisposing to heat stroke in the elderly. Cardiovascular factors are very important in protecting against heat. The cutaneous vasodilatation and consequent adjustments in blood flow are impaired in the presence of heart failure. Even when there is no overt heat disease, heart failure can occur with severe heat stress. Elevated central venous pressures have been recorded in young men with heat stroke even though the cardiac output was capable of increasing to more than twice normal values.[7] Several studies have shown that, unlike normal subjects, patients with severe cardiac disease do not increase their tolerance to heat with time. These patients, all of whom had class III or IV cardiac disease, had impaired sweat production, greater subjective discomfort, and little or no increase in heart rate or cardiac output compared to subjects without cardiac disease. During exposure to heat, the patients exhibited dyspnea, with increased venous pressure, rales, and gallop rhythm. Most of the patients were unable to tolerate temperatures in excess of 90°F and 41 per cent humidity.[3] The marked increase in respiratory rate which was observed, while related to increasing heart failure, is also a physiologically sound modification of heat adaptation in cardiac failure since evaporation as well as direct cooling of congested lungs will occur as long as adequate ventilation can be maintained. Panting is an efficient means of cooling and in most mammals is the only means of cooling at high temperatures.

Many other factors also predispose to heat stroke. Therapy with diuretics predisposes to heat stroke by preventing volume expansion and thereby limiting cutaneous vasodilatation. Anticholinergic agents predispose to heat stroke by inhibiting sweating. Another disease state associated with increased risk of heat stroke among the elderly is Parkinson's disease. The muscular work performed by these patients is considerable, and many of the medications used to treat this disorder have atropine-like effects so that sweating is impaired. Dermatologic disease of any type, if it affects a large area of skin, may be associated with decreased or absent sweating of the affected areas. Patients with spinal cord lesions, as mentioned earlier, also have impaired temperature-induced sweating because the pathways from the hypothalamus to the skin have been interrupted. Bedridden, senile patients may be unable to throw off bedclothes or maintain volume expansion through voluntary fluid intake. Surgical patients are likewise subjected to heavy draping which they cannot remove and, in addition, they may have been given atropine preoperatively. Obesity, because of the increased mass-to-surface-area ratio and the increased muscular work required for all activities, is also a risk factor. Alcohol intoxication, though more often seen in younger age groups, is by no means unknown in the elderly. Very modest intake of alcohol increases metabolic work, promotes diuresis, impairs vasomotor control, and may also seriously impair the individual's judgment. Acute infection of viral or bacterial origin not infrequently precedes the development of heat stroke. The fever caused by the infection increases the dangers of heat exposure; in an individual with fever of 102 to 103°F, only 2 or 3 degrees of further elevation due to heat exposure may result in heat stroke.

Clinical Features

Often very little history is obtained from victims of heat stroke because they present in a comatose state. When a history is obtained, usually from a friend or relative, there may be a prodromal period of a day or so of lethargy, fatigue, or weakness, sometimes associated with dizziness, nausea, and vomiting. More often, the patient will have had no prior complaints and will have been stricken quite abruptly.

The diagnosis of heat stroke is made when fever, usually in excess of 103°F and frequently in excess of 106°F, results after exposure to heat. The absence of sweating is often seen and, when present, is an invaluable diagnostic aid. Patients with heat stroke present with varying degrees of impairment of consciousness such as lethargy, stupor, or coma. Convulsions may also occur. Another clinical feature often associated with heat stroke is hyperpnea, which may be pronounced and may result in the misdiagnosis of pneumonia, particularly when rales are heard. The hyperventilation may be further intensified by shock or acidosis.

Modest elevations in the blood urea nitrogen of 20 to 40 mg per 100 ml are not infrequent. Acute renal failure and jaundice are sometimes seen in very seriously affected patients who survive. Muscle necrosis, as mentioned previously, is seen in young victims. Dehydration is a variable finding in heat stroke and tends to be overdiagnosed because of the presence of dry skin which is often incorrectly attributed to excessive fluid loss. In reports of heat stroke affecting chiefly the elderly, coexisting dehydration was seen in 10 to 20 per cent of cases.[1,5] A bleeding diathesis may occur; petechial hemorrhages in the skin are often seen and occur throughout the body. In more seriously affected cases, gastrointestinal bleeding is seen. This feature of heat stroke, recognized clinically for many years, has recently been restudied and found to be due to disseminated intravascular coagulation.[9]

A series of 12 patients who died of heat stroke at Coney Island Hospital illustrates some of these points. All patients were over the age of 66, and 6 of them were in their 80's. Five were known to be taking diuretics and 2 were taking digitalis. Four were obese. Three of these patients were already hospitalized and were seriously ill at the time they were affected. Temperatures of 104 to 110°F were recorded, and 10 of the 12 were noted to have respiratory distress or hyperpnea, often with rales or rhonchi. Two patients had a serum sodium of over 150 mEq/L.

Another series of 6 patients who were admitted during a different heat wave were specifically studied for bleeding disorders; 4 were noted to have evidence of bleeding in the skin. All of these patients had thrombocytopenia of some degree at some time in their course. Three patients, including the 2 who died, had fibrin-split products in the blood and 1 patient, a 90 year old woman admitted with a temperature of 109°F, also had fragmented red cells seen on peripheral smear. This patient received a continuous heparin infusion and responded initially but expired of pneumonia 27 days later.

Pathology

The most striking pathological changes in fatal heat stroke are seen in the brain. Diffuse petechial hemorrhages occur. There is no evidence to suggest that the hypothalamus is selectively involved; in fact it appears to be relatively spared. In patients dying within the first few hours edema and congestion are present, and in patients surviving 18 hours or more, irreversible damage to neurons with necrosis occurs. These cellular changes are the direct effect of heat, probably resulting from protein denaturation and coagulation. Elsewhere, pathologic changes consist chiefly of diffuse petechial hemorrhages, or are the result of shock. In patients with a clinical bleeding diathesis, widespread hemorrhages are seen particularly involving the lungs and also the heart, the gastrointestinal tract, and other organs. Hepatocellular necrosis of the liver and tubular damage in the kidneys, changes similar to those known to occur in shock, may develop in patients who survive the first few days.[6]

Therapy

Because the elevation in body temperature is the cause of the disorder, rapid reduction of body temperature is regarded as the cornerstone of therapy. However, many methods have been proposed for cooling.[4,5]

In some reported series, patients were treated by being generously sponged with cool water or lightly wrapped in wet towels, and placed directly in the path of a strong fan. This form of treatment has the advantages of being easy to perform and requiring only readily available equipment. Further examination and treatment can be carried out during the process of cooling.

An alternate means of therapy, recommended by many, involves immersing the patient in a bath of cold water. This method is very rapid but awkward and it requires constant rubbing of the skin of the extremities to maintain cutaneous vasodilatation. If shivering occurs, heat loss is considerably retarded. However, shivering may be inhibited by intravenous thorazine in doses of 25 to 50 mg. We have found this method to be useful, particularly in comatose patients who do not shiver. Since epidemics of heat stroke are not difficult to predict, baths can be made ready in advance. Our overall survival rate in heat stroke appears comparable to the rate in institutions using other methods. Cooling the patient in an air-conditioned room is effective only for relatively minor hyperpyrexia and minor clinical symptoms. Bizarre and time-consuming methods of cooling such as ice-water enemas are relatively inefficient and unnecessary. The use of standard antipyretic drugs such as aspirin or acetaminophen is not helpful because their action requires the presence of intact heat losing mechanisms, and may be harmful because of their tendency to produce bleeding.

External cooling should be carried out until the patient's temperature falls to 102°F and then discontinued, as a further fall of several degrees can be expected. Secondary rises in temperature may occur requiring additional external cooling. In fact the patient's temperature may remain unstable for several days.

Treatment of any complicating features of heat stroke should begin immediately. Oxygen should be given to supply the hypermetabolic tissue needs and shock, acidosis, infection, or cardiac failure if present must also be treated. If bleeding is clinically apparent, transfusion of blood or clotting factors may also be necessary. At present, heparin is not recommended for the treatment of disseminated intravascular coagulation. Excessive amounts of intravenous fluid should be avoided unless obvious clinical dehydration exists because pulmonary edema can result from overhydration. Since patients may present with high, low, or normal serum sodium levels, the type of fluid used must be determined by the clinical and laboratory findings. Serial measurements of the serum sodium and proteins are often helpful in judging the need for fluid replacement. Blood volume measurements, if readily available, will also be helpful.

The mortality in heat stroke rises with increasing duration and degree of hyperpyrexia, being especially high when the body temperature rises to 108°F or higher. Coma and shock are associated with a higher mortality rate, and so is severe hyperkalemia.

Heat stroke can be prevented rather simply. The elderly and their families should be made aware of the danger and instructed to decrease physical activity during hot weather. Light, loose clothing should be worn. Air conditioning, if available, should be used. Bathing, showering, or sponging with cool water is useful if the living quarters cannot be made cooler by other means.

Since chronically ill patients in hospitals and nursing homes are also at risk, the body temperature, mental status, and the presence or absence of sweating should be recorded frequently, and restrictive coverings removed. Occasional sponging of patients at high risk may be necessary under severe conditions. Operating rooms that are not air conditioned should not be used for elective surgery when the temperature for the day is expected to exceed 90°F.

The physician in charge of the emergency room should re-instruct all personnel annually on the prompt recognition and treatment of heat stroke, and make sure that all necessary equipment is readily available.

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Division of Endocrinology and Metabolism
Coney Island Hospital
2601 Ocean Parkway
Brooklyn, New York 11235

Changes in Behavior, Mood, or Thinking in the Elderly

Diagnosis and Management

Lewis Glickman, M.D., [*] *and*
Sandor A. Friedman, M.D., F.A.C.P.[**]

Changes in mood, behavior, and thinking are frequently found among the elderly. Although most adjust to growing older, a combination of decreasing cognitive function, isolation, and drastic changes in well-established patterns of life style may lead to a spectrum of disorders. In these patients it is often difficult to separate the changes resulting from organic causes from those which have psychological causes. Therefore careful evaluation of the medical, psychological, and social conditions is essential before therapy can be planned.

The first priority, when evaluating a patient with recent personality changes, is to try to ascertain suicidal risk, to which the elderly are especially prone.[2,4,5] Suicide in men increases with each decade; in the eighth decade it is three times as frequent as in the third decade. Loss of health, death of a spouse, retirement, and children marrying and moving away are frequent precipitants of depressions of suicidal proportions. Approximately one in four suicides is committed with sedatives prescribed by a physician, and two thirds of suicidal patients have consulted a physician in the 6 months prior to their death.

Often, because of denial or memory deficit or both, a history from relatives is necessary to ascertain suicidal or homicidal risk. This is especially true when the relative has arranged the appointment or accompanies the patient. The relative should be interviewed in the presence of the patient. This will allow the physician to observe the relationship between the two, will prevent the patient from seeing the physician as the relative's agent rather than as his own, and will allow the physician to confront the patient with the facts provided by his relative.

If homicidal or suicidal risk is suspected, psychiatric consultation and/or hospitalization either in a general or psychiatric hospital is necessary. Even the most agitated and belligerent patient can be treated on a general medical service if he will allow parenteral injections to be given. Treating the patient on a medical service has the advantage of providing the optimal environment for the diagnosis and treatment of associated or etiologic medical or neurologic disease. If the patient refuses medication, hospitalization in a psychiatric unit is necessary. On hospitalization, the physician should make it clear to the patient that he does not believe that he is insane; rather he is concerned that he will harm himself in his present frame of mind. He should also point out that hospitalization will allow a more complete diagnosis to be made and treatment to be carried out more rapidly and effectively.

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[*] Assistant Professor of Psychiatry, Downstate Medical Center; Liaison Coordinator, Coney Island Hospital, Brooklyn, New York

[**] Chief of Medical Services and Chief of Peripheral Vascular Disease Division, Coney Island Hospital; Associate Professor of Medicine, State University of New York, Downstate Medical Center

ORGANIC BRAIN SYNDROME

Whether or not the patient is a homicidal or suicidal risk, the possibility of organic brain syndrome should be considered in anyone over 40 years of age with a recent change in thinking, mood, or behavior. Differential diagnosis between organic brain syndrome and a functional psychiatric disorder, as well as among the various causes of organic brain syndrome, is made on the basis of history, mental status, physical examination, and laboratory studies.

Both the relatives and the patient should be asked about headaches, nausea, vomiting, fainting or falling, ataxia, seizures, incontinence, memory loss, and lack of concern for personal hygiene or for the state of the patient's home, if he lives alone. The presence of any of these factors strongly suggests an organic etiology, regardless of what other psychiatric abnormalities may also be present.

Abnormal episodes with normal intervals suggest transient ischemic attacks, Stokes Adams attacks, or hypoglycemia.

A dietary, alcohol, drug, and medication history is also extremely important. Malnutrition, with or without associated alcoholism, as well as many commonly prescribed medications, may cause organic brain syndrome. Alcoholism or abuse of sedatives or minor tranquilizers can produce organic brain syndrome as a result of either direct toxicity or withdrawal in those patients who have become physically dependent. Many commonly prescribed drugs are more likely to produce delirium in the elderly than in younger patients. These include digitalis, phenytoin (Dilantin), antidepressants—especially the so-called fast-acting ones such as desipramine (Norpramine)—as well as L-Dopa, steroids, lidocaine, pentazocine (Talwin), and propranolol (Inderal).

The first sign of abnormality is often of great diagnostic significance. For example, if memory deficit *antedates* depression, the cause is extremely likely to be organic, and the depression is likely to be a reaction to the memory loss. If depression antedates memory deficits, it is likely that the loss of memory is a pseudo deficit caused by apathy or lack of interest. Depression may also cause anorexia and malnutrition leading to organic brain syndrome secondary to thiamine deficiency (Wernicke-Korsakoff encephalopathy). Similarly, depressed patients may take prescribed medications incorrectly.

All organic brain syndromes are found in combination with a functional component because patients react emotionally when they become aware of the deterioration in their intellectual function. The extent and type of emotional reaction depends on three factors: preexisting personality structure, the speed of development of impairment, and the extent of the organic impairment. The emotional component is not related to the cause of the organic brain syndrome. Patients may become depressed, suicidal, paranoid, assaultive, anxious, or fearful, whatever the cause. These are called positive or breakthrough symptoms; they are often dramatic and sometimes dangerous. They may deflect the physician's attention from the pathognomonic symptoms of organic brain syndrome: memory loss, disorientation, and decrease in level of consciousness. Breakthrough symptoms are usually identical with those found in functional psychiatric illness. Two breakthrough symptoms, however, are useful in making a differential diagnosis between functional psychiatric illness and organic brain syndrome. Those are visual hallucinations and auditory hallucinations whose source is within the ordinary range of hearing.

The diagnosis of organic brain syndrome can be made with some certainty by the nonpsychiatric physician who evaluates intellectual function, level of wakefulness, and motor function. Those aspects of brain function which are last acquired in the life history of the individual and in the development of the species are the first to be lost in organic brain syndrome. Intellectual function is last acquired and therefore is the first to be lost. Intellectual deficits can be ascertained by the clinician through testing memory, ability to calculate, and concentration span. The highest cognitive faculty is the ability to think abstractly. This is the first to be lost and can be tested on mental status examination by tests of similarities and interpretation of proverbs. However, these tests are not usually helpful in differential diagnosis since performance is decreased in patients with low intelligence or schizophrenia as well as with organic brain syndrome.

The next cognitive faculty to be lost is memory, starting with the most recent. Memory is not as closely dependent on intelligence quotient as ability to abstract, and is not damaged in any functional psychiatric disorder. The patient with memory loss frequently does not complain of it but displaces his concern to another symptom. The physician, therefore, should evaluate cognitive function in every elderly patient who consults him just as he evaluates cardiac function. A memory deficit will often be revealed to the clinician, if the patient's chronological account of his illness is inconsistent and contradictory. Formal testing may be necessary to ascertain recent memory deficit. The physician should explain to the patient that as part of his examination he would like to test his memory. He should then give the patient four numbers to remember, ask him to repeat the four numbers backward and to again repeat them five minutes later. The patient should also be asked to subtract 7 from 100 and to subtract 7 from his answer out loud as fast as he can. Anyone who has completed the sixth grade should be able to complete both these tasks correctly if he is willing to cooperate, is not handicapped in his ability to concentrate by severe anxiety or depression, and does not have an organic brain syndrome. Often patients with cognitive deficits try to cover over their defects by becoming angry, tearful, or jocular when asked to perform tasks that they cannot successfully complete. Depressed patients with psychomotor retardation will generally answer correctly but require a longer time to complete the tasks.

In some cases it is impossible to differentiate organic brain syndrome from a severe depression on mental status examination. In these instances laboratory procedures are necessary. Occasionally a brain tumor or other localized lesion may manifest itself with no memory deficit but as a classical depression.

Orientation is generally lost after memory for recent events. Orientation for time is lost first, followed by orientation for place and finally for person. Orientation for time is lost in the order of day or date, month, and year. Since one usually has a longer time to learn what month it is than to learn what day it is, the month is less easily forgotten.

Level of consciousness is ascertained by inspection of the patient. In the absence of sedation or tranquilization, apathy or lethargy should arouse suspicion of organic brain syndrome. Somnolence or stupor almost always indicates organic brain syndrome. If the physician is uncertain whether the patient's level of wakefulness is decreased, he should ask the accompanying relative if the patient appears lethargic or sleepy. Slurred speech is often associated with lethargy or somnolence due to organic brain syndrome and very rarely present in functional psychiatric illness.

Certain physical findings are of great help in diagnosing organic brain syndrome. Asterixis, myoclonic twitching, and/or coarse tremor are found at some time in the course of almost any metabolic encephalopathy. Asterixis is best elicited when the patient is asked to extend both arms straight ahead and to hyperextend his hands at his wrist while holding his fingers as far apart as possible. After a few seconds there will appear a rapid, coarse, asymmetric vertical movement of the hand at the wrist, irregular in amplitude and in timing. Occasionally there is a coarse, regular tremor, or lateral movement of the hands at the wrist. Variation in respiratory rate or depth (respiratory ataxia) may be a sign of cerebral dysfunction due to primary brain disease, hypoxia, inadequate cerebral blood flow, or other metabolic imbalance.

Obviously, the presence of systemic disease such as cirrhosis, uremia, or anemia or the finding of focal neurologic signs points strongly to organic brain syndrome. It is particularly important to look for frontal lobe signs such as exaggerated jaw jerk, sucking and grasp reflexes, and ataxic gait.

The most useful screening test to differentiate between organic brain syndrome and functional psychiatric disorder is the electroencephalogram. It is almost always abnormal in organic brain syndrome except early in senility and in half the patients with Wernicke-Korsakoff encephalopathy. The electroencephalogram is also useful in differentiating between the metabolic encephalopathies on the one hand and localized central nervous system disease such as vascular and space-occupying lesions on the other. The electroencephalogram will be diffusely slowed in metabolic encephalopathy, whereas in localized cerebral disease it will usually show focal abnormalities. All other laboratory tests are more useful in ascertaining the cause of the organic brain syndrome than as screening tests for the presence of organic brain syndrome. These will be discussed below.

The separation of organic brain disease from pure psychiatric illness is only the first diagnostic step. Unfortunately, many elderly patients are labelled with the diagnosis of organic brain syndrome as though it denoted a specific entity. This is analogous to telling a patient with dyspnea that he has something wrong with his heart or lungs. One must not fall into the trap of automatically equating decreasing mental function in an older individual with cerebral arteriosclerosis or senile dementia. The latter two can be diagnosed only after a complete evaluation of the patient has ruled out other possible etiologies.

A detailed discussion of all the possible causes of failing mental function is beyond the scope of this article. However, the outline in Table 1 contains many of the possible causes of organic brain syndrome in the elderly with an emphasis on amenability to treatment and predilection for elderly subjects. In any patient with changes in cerebration, there are certain laboratory tests which should be performed even if physical examination has revealed no evidence of systemic disease or focal neurologic signs. These include complete blood count, fasting blood sugar level, blood urea nitrogen, serum electrolyte concentrations, plasma thyroxine concentration, serum calcium level, radionucleotide brain scan, electrocardiogram, and electroencephalogram. A decision to proceed with additional tests should be based on the clinical and laboratory findings.

For example intermittent episodes of disordered thinking or inappropriate behavior should suggest four diagnostic possibilities. Although both senile dementia and cerebral arteriosclerosis commonly produce exacerbations and remissions, other more treatable entities must be considered.

Hypoglycemia may appear without any of the adrenalin-response symptoms and result in psychotic behavior, loss of cognitive function, or both. Not infrequently, episodic hypoglycemia is the result of overzealous therapy for diabetes mellitus. Blood sugar determinations obtained during the episodes of abnormal behavior are most helpful in making the diagnosis.

Changes in cardiac rhythm are notorious for presenting with cerebral signs and symptoms. Electrocardiographic monitoring of patients during their normal activities may lead to the discovery of transient and preventable arrhythmias.

Transient ischemic attacks are also characterized by episodes of confusion, as are subdural hematomas.

The entities that occur frequently and insidiously in the elderly, which merit particular emphasis include the following.

Hypothyroidism

A level of thyroid function that might result in a virtually asymptomatic younger individual may lead to mental slowness and lethargy in the elderly. Skin changes of myxedema and bradycardia may

Table 1. *Differential Diagnosis of Organic Brain Syndrome*

CATEGORY	SYNDROME	COMMON ETIOLOGY
Endocrine-metabolic	Hypothyroidism	Autoimmune
	Hypoglycemia	Alcoholism Liver disease Insulin and hypoglycemic agents Islet cell tumor of pancreas
	Hypercalcemia	Hyperparathyroidism Neoplastic disease Multiple myeloma Sarcoidosis
Electrolyte abnormalities	True hyponatremia	SIADH Diuretic therapy Renal tubular disease Adrenal insufficiency
	Relative hyponatremia	Edematous states
	Metabolic acidosis	Uremia Renal tubular acidosis Chronic diarrhea Ketoacidosis Lactic acidosis
	Metabolic alkalosis	Diuretic therapy Hyperadrenalism
	Hyperosmolar states	Diabetes mellitus Excessive water loss

Metabolic	Hepatic encephalopathy	Liver disease decompensated by hypokalemia, acidosis, alkalosis, gastrointestinal bleeding, dehydration, or systemic infection
	Uremia	Chronic glomerulonephritis Chronic pyelonephritis Diabetic nephropathy Obstructive uropathy
	CO_2 intoxication	Chronic obstructive pulmonary disease often aggravated by dehydration, diuretic therapy, or respiratory infection
Nutritional	Thiamine deficiency	Alcoholism Malnutrition
	Vitamin B_{12} deficiency	Pernicious anemia Malabsorption syndrome (e.g. regional enteritis)
	Pellagra	Inadequate dietary intake
Anemia	Folate deficiency	Inadequate dietary intake Malabsorption
	Iron deficiency	Gastrointestinal bleeding
	Hypoplastic anemia	Chronic systemic disease Drug toxicities
	Bone marrow infiltration	Luekemias and metastatic carcinoma

Table 1. *Differential Diagnosis of Organic Brain Syndrome*

CATEGORY	SYNDROME	COMMON ETIOLOGY
Circulatory	Heart failure with low cardiac output	Arteriosclerotic heart disease Hypertensive heart disease Papillary muscle dysfunction Aortic stenosis, amyloidosis
	Intermittent tachycardias or bradycardias	Sick sinus syndrome Atrioventricular nodal disease Abnormalities in potassium concentration, digitalis toxicity
	Orthostatic hypotension	Antihypertensive drugs Diabetic neuropathy Brain stem disease Adrenal insufficiency
	Cerebral emboli	Mural ventricular thrombosis Atrial thrombi with atrial fibrillation Platelet and atheromatous emboli from cerebral vessels (e.g. internal carotid artery)
	Coagulopathy	Thrombocytosis Disseminated intravascular coagulation
	Cerebrovascular disease	Arteriosclerosis Cranial arteritis

Sensory deprivation	Hearing loss and poor vision	Otosclerosis Cataracts
Drugs	Sedation	Sedatives and tranquilizers
	Dehydration and hyponatremia	Diuretics
	Hypoglycemia	Hypoglycemic agents
	Orthostatic hypotension	Antihypertensive medications
	Cerebral atrophy	Alcohol
Central nervous system disease	Primary tumors	
	Metastic carcinoma	Breast carcinoma Bronchogenic carcinoma Hypernephroma
	Tuberculous meningitis	
	Fungal meningitis	Cryptococcus
	Brain abscess	
	Chronic subdural hematoma	Anticoagulation Trauma
	Normal pressure hydrocephalus	Sometimes associated with trauma Unknown
	Senile dementia	Unknown
Systemic infection	Subacute bacterial endocarditis	
	Tuberculosis	

be absent. A delayed relaxation phase of deep tendon reflexes may be the only clinical clue. Unusual slowness in body movements, deepening of the voice, signs of carpal tunnel syndrome or cold hands and feet in a patient with decreasing mental function should lead to a full thyroid evaluation.

Inappropriate Secretion of Antidiuretic Hormone

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is more common in the elderly for several reasons. Organic brain syndrome, regardless of etiology, increases susceptibility to SIADH. Patients with mild chronic brain syndrome may dramatically deteriorate with the development of hyponatremia. Other factors leading to this syndrome which are frequent in the elderly include hypothyroidism, diuretic or chlorpropamide therapy, certain malignancies and systemic infection. Even severe pain, as seen in osteoarthritis, may stimulate excessive secretion of ADH in an elderly person. The cardinal features of the inappropriate ADH syndrome include hyponatremia, lack of edema, and a normal blood urea nitrogen level—all reflecting an expanded blood volume without salt retention. When the serum sodium concentration falls below 120 mEq per 100 ml, plasma osmolality may become low enough to lead to water intoxication of brain tissue and signs of decreased mentation. Therapy consists of water restriction and correction, where possible, of the underlying precipitating factors.

Malnutrition

Malnutrition in the elderly is also a frequently overlooked problem. Many elderly individuals eat a vitamin-deficient diet because they live alone, are somewhat depressed or mildly confused and therefore indifferent to or forgetful about meals. Vitamins, the lack of which may result in organic brain syndrome, include thiamine, niacin, folic acid, and vitamin B_{12}. Folic acid or Vitamin B_{12} deficiency may cause mental changes even in the absence of anemia. Of all these factors, the insidious development of megaloblastic anemia secondary to folate deficiency is the most common nutritional problem.

Peripheral neuropathy in the absence of diabetes mellitus and uremia should alert the clinician to the possibility of thiamine deficiency. Thiamine deficiency may also present with the so-called Wernicke's triad of apathetic confusion, ataxia, and eye signs, the most common of which are nystagmus and lateral deviation of the eye. This syndrome is due to damage of cells in the lower pons and upper midbrain including the mamillary bodies, oculomotor nuclei, and superior colliculi. When thiamine is restored to the diet, the eye signs and ataxia disappear in several days to weeks, but memory returns completely in only one third of patients, partially in one third, and not at all in another third. Memory may continue to improve after months or even one or two years. When the patient is fully awake and has only a memory deficit, the clinical picture is called the Korsakoff syndrome. It is often characterized by the patient's attempt to hide his memory deficit by confabulation.

Normal Pressure Hydrocephalus

Normal pressure hydrocephalus is characterized by dilatation of the lateral ventricles and decrease in size of the supracortical cerebrospinal fluid space. The ventricular system is enlarged because of decreased absorption of cerebrospinal fluid space by the paccionian corpuscles. The clinical picture is that of an organic brain syndrome often accompanied by ataxia and incontinence. Although the etiology is not well understood, this condition sometimes follows trauma, subarachnoid hemorrhage, cerebrovascular accident, or intracranial surgery. It can also occur without known cause. It is extremely important to consider this diagnosis in all patients with organic brain syndrome of unknown etiology because it can often be arrested by ventricular shunting procedures.[6] Computerized axial tomography (CAT) has provided a simple and ready means of diagnosis. If this procedure is not available, one must strongly consider performing either a pneumoencephalogram or a radionucleotide scan of the ventricular system in all patients with organic brain syndrome of unknown cause, especially if accompanied by ataxia.

Computerized axial tomography promises to become more widespread as the equipment becomes more generally available.[1] The system produces a series of tomograms of the brain and is capable of detecting small intracranial lesions as well as cerebral atrophy, infarct and hemorrhage. Where it has been introduced, the necessity for invasive procedures such as cerebral angiography and pneumoencephalography has been greatly reduced.

TREATMENT OF FUNCTIONAL SYMPTOMS

The most frequent functional psychiatric disorder in the elderly is depression. Depression is most often precipitated by loss of a relationship with the important person in the patient's life such as a spouse or child. Etiologic treatment should be directed at providing a substitute for the lost relationship, as the patient attributes to the physician the qualities of the person he has lost. Havens has described this type of treatment of depression as "social nutrition." The nonpsychiatric physician is often in a better position than the psychiatrist to manage such therapy of the elderly patient for two reasons: he is more acceptable to the patient, and he can treat the associated somatic illnesses. These patients are sometimes referred to psychiatrists simply because their physicians are not convinced of the value of the doctor-patient relationship. The referral can exacerbate the depression because the patient may experience it as an additional loss.

Referral of depressed patients to Senior Citizens Centers is harmful as part of an *initial* therapeutic plan because the patients are too preoccupied with themselves to benefit from exposure to the possibility of forming new relationships. Failure to form new relationships further diminishes their self-esteem. Senior Citizens Centers are useful to help prevent future relapses *after* depressive episodes have been effectively treated.

The physician should offer the depressed patient sympathy and support, both of which are helpful whether the patient is reacting to increasing disability because of the irreversible progression of a disease or because of the death of a spouse. It is important for the physician to tell the patient that he understands how difficult it must be for him to manage and that anyone in his circumstances would find it equally difficult. The patient should be assured that he is adjusting better than many and that the physician will continue to help him cope with the problem. Many patients experience relief of symptoms from placebos even when an organic process continues unabated. Even with the progression of organic disease, anxiety or depression may be abated if the physician maintains a regular relationship. On the other hand, merely advising the patient to learn to live with his disability often provokes guilt and increased loss of self esteem because he is unable to follow the doctor's advice. The patient is often troubled less by the objective reality of the increasing impairment than by the meaning to him of his impaired function. He may interpret his impaired function as meaning he is worthless, hopeless, and alone. If the physician continues to see and treat the patient on a regular basis, most often these feelings can be counteracted regardless of the lack of objective improvement in the accompanying organic disease. It is as if the patient says to himself, "As long as the doctor cares about me, I am worth caring about; as long as he's with me, I'm not alone; as long as he treats me, my case isn't hopeless."

SYMPTOMATIC TREATMENT

In addition to psychotherapy, psychotropic drugs are effective in the treatment of certain target symptoms regardless of whether these symptoms are associated with an organic brain syndrome or a functional psychiatric disorder. Although psychotropic drugs are divided into five types (Table 2) the psychopharmacologic management of the elderly rests on two classes of drugs: the major tranquilizers (neuroleptics, antipsychotics) and the antidepressants (mood elevators, psychic energizers).[3]

Anxiety, agitation, and hyperactivity will respond to minor as well as to major tranquilizers and sedatives. Minor tranquilizers, however, have an unacceptably high risk-benefit ratio when used in the chronic treatment of the aged. Even in young patients, when the minor tranquilizers are used for the control of severe symptoms, doses large enough to cause an acute brain syndrome with decreased cognition, level of consciousness, and coordination may be necessary. Patients also develop tolerance to their therapeutic effects. Although it is rare for elderly patients to increase the dose on their own, they may occasionally do so, and thereby risk the development of physical dependence and a possible withdrawal syndrome. Some elderly patients are extremely sensitive to minor tranquilizers and develop ataxia and prolonged stupor on doses which are safe for younger adults.

Depressed patients should not be given sedatives because of the

Table 2 *Classification of Psychotropic Drugs*

MAJOR TRANQUILIZERS (ANTIPSYCHOTICS, NEUROLEPTICS)	MINOR TRANQUILIZERS (ANTI-ANXIETY AGENTS)	SEDATIVES (HYPNOTICS)	ANTIDEPRESSANTS (PSYCHIC ENERGIZERS)	STIMULANTS
Phenothiazines	*Benzodiazepines*	*Older Agents*	*Tricyclics*	*Amphetamines*
Thorazine	Valium	Paraldehyde	Tofranil	Dexedrine
Stelazine	Librium	Chloral Hydrate	Elavil	
Mellaril	Serax	Barbiturates	Sinequan	
Prolixin or Permitil	Dalmane			
Thioxanthenes	*Hydroxyzines*	*Newer Agents*	*"Fast-Acting" Tricyclics*	*Non-amphetamine*
Taractan	Atarax	Doriden	Norpramine or Pertofrane	Ritalin
Navane	Vistaril	Placidyl	Aventyl	Preludin
		Noludar	Vivactyl	
		Quaalude	*Monamine Oxidase (MAO) Inhibitors*	
Butyrophenones	*Meprobamate*			
Haldol	Miltown or Equanil		Marplan	
			Parnate	
Dihydroindolones				
Moban				

danger that they may use them to commit suicide. Sedatives, like minor tranquilizers, may also cause paradoxical excitement in the elderly. Sleeplessness can be effectively treated with single nightly doses of major tranquilizers or antidepressants.

Sedatives and minor tranquilizers do have one advantage over the major tranquilizers. They do not produce hypotension and can be given intravenously for control of severe agitation. Intravenous diazepam (Valium) or intravenous amobarbital (Amytal), however, should not be used unless the physician is able to intubate the patient and provide assisted respiration because of the possibility of laryngospasm and respiratory depression. Major tranquilizers cannot be given intravenously to control agitation because of their tendency to produce hypotension. Even when major tranquilizers are given intramuscularly, the patient must be kept in bed. Doses must be gradually increased over several days until a therapeutic level is achieved. Blood pressure should be checked before and one-half hour after each intramuscular dose of a major tranquilizer.

Within each class of psychotropic drug, all are, as a rule, equally efficacious, but differ in their side effects. For example, chlorpromazine (Thorazine) and thioridazine (Mellaril) are more likely to lower blood pressure, but are less likely to cause extrapyramidal signs such as pseudo-parkinsonism, akathasia, dystonia, and dyskinesia than are the other major tranquilizers. Target symptoms responding to the various psychotropic drugs are listed in Table 3, and their side effects are summarized in Table 4. The principles of psychotropic drug use in the elderly and young are identical, but smaller starting doses and slower rates of increment must be used in the former.

The principles are:

1. Choose an appropriate target symptom. If there is more than one symptom, choose the one which is most dangerous, disabling, or unacceptable to the patient. Choose one drug useful in the treatment of this symptom.
2. Begin with a low dose and increase slowly either until side effects occur which are more dangerous or disabling or unacceptable to the patient than the original symptom, or until the symptom is controlled.
3. If serious side effects develop, switch to another drug in the same class and begin as before.
4. If additional target symptoms remain after the target symptom is controlled, add another drug and begin as before.
5. After all the target symptoms are controlled, gradually reduce the dose of one drug until either the target symptom recurs or until the dose reaches zero, and then do the same with the other drug.

All psychotropic drugs have an initial dose, a therapeutic dose, and a maintenance dose which must be determined for each patient. The initial dose is determined by the likelihood of side effects; the therapeutic and maintenance doses by the response of the target symptoms. The initial dose in the elderly is generally about 40 per cent of the initial dose in younger adults. Hypotension, ataxia, stupor, toxic delirium, and cardiac arrhythmias are all more likely in the elderly. Therapeutic and maintenance doses may be the same both for the elderly and younger

Table 3. *Target Symptoms of Psychotropic Drugs*

	ANXIETY FEARFULNESS	ANGER ASSAULTIVENESS	APATHY DISINTEREST INACTIVITY	SADNESS	AGITATION HYPERACTIVITY	EUPHORIA
Major tranquilizers	++	++	0	0	++	++
Minor tranquilizers	++	++	0	0	++	++
Sedatives	++	++	0	0	++	++
Antidepressants	0	0	++	++	0	0
Stimulants	0	0	++	++	0	0

Table 4. *Side Effects of Psychotropic Drugs*

	WAKEFULNESS	INTELLECTUAL FUNCTIONING	ADDICTION	LETHALITY	CARDIAC ARRHYTHMIAS	TOLERANCE TO THERAPEUTIC EFFECT	HYPOTENSION	DYSKINESIA DYSTONIA, AKATHASIA	DELIRIUM	ATAXIA STUPOR
Major tranquilizers	↓ (Initially)	0	0	0	0	0	++	++	0	0
Minor tranquilizers	↓↓	↓	+	+	0	++	0	0	+	++
Sedatives	↓↓	↓↓	++	++	0	++	0	0	+	++
Anti-Depressants	↓ (Initially)	0	0	+++	++	0	++	0	+	0
Stimulants	0	↓	++	+	+	++	0	0	+	0

adults, but should be approached more slowly in the elderly. Most failures to respond are due to inadequate dosage rather than to choice of wrong drug. Switching from one drug to another is generally necessary only in the event of serious side effects.

The elderly are sensitive to all dose-related side effects, especially those such as the sedative, hypotensive, anticholinergic, and extrapyramidal effects, to which tolerance gradually develops. If small doses and gradual increments are used, these either will not appear or will spontaneously disappear as homeostasis develops. Postural hypotension is the most important side effect since the development of hypotension limits the rapidity with which both the antidepressants and the major tranquilizers may be increased. While dosage is being increased, patients should be warned to move slowly, holding on to something for support when changing from a lying to sitting or from a sitting to standing position. The hypotensive and sedative effect should disappear within a week or 10 days after the maximal dose is reached. Anticholinergic side effects may cause difficulty in focusing and dry mouth. The development of these symptoms may cause the patient to skip medication. Acute glaucoma may be precipitated in a patient with undetected disease. Treated glaucoma has not been reported to be exacerbated by psychotropic drugs.

Extrapyramidal side effects may occur with the major tranquilizers, but usually subside after decreasing the dose. Anti-Parkinson agents can be used prophylactically, but they will increase the likelihood of anticholinergic side effects such as urinary retention, toxic deliria, paralytic ileus, and heat stroke due to inhibition of sweating. If anti-Parkinson agents are used, they can be discontinued in 70 per cent of patients in 3 months without recurrence of symptoms.

When one of the above-mentioned side effects is severe, another drug in the same class should be tried. The new agent should be the one which is least likely to produce that side effect. If idiosyncratic reactions develop, such as cholestatic jaundice in the case of phenothiazines, the patient should be switched to a chemically different agent. For example, a butyrophenone such as haloperidol (Haldol) may be substituted for a phenothiazine.

The most frequent instance in which two classes of psychotropic drug are necessary is the agitated depression. If restlessness and irritability are brought under control by a major tranquilizer and the patient continues to evidence a depressive effect and lack of interest in activities he formerly enjoyed, an antidepressant should be added and gradually increased until these symptoms are alleviated. With many patients antidepressants are not necessary, as the depression either responds to the major tranquilizer or disappears spontaneously while the other symptoms are being alleviated.

The lowest possible maintenance dose is especially important in the case of major tranquilizers in order to prevent the development of tardive dyskinesia and pigment deposition in the eye and skin. The elderly are especially prone to develop tardive dyskinesia (buccal-lingual masticatory syndrome). This usually develops after years, but sometimes after only months of treatment. The syndrome is characterized by choreiform movements of the jaw, mouth, tongue, and sometimes the shoulder girdle. These movements seriously interfere with speaking, eating, and swallowing and can cause death through inanition. The treatment of tardive dyskinesia is far from satisfactory. Only about half the patients respond to withdrawal of major tranquilizers. Some of the others respond to increasing the dose of major tranquilizer, but this leaves the patient susceptible to a recurrence. No other medication is helpful.

Reduction of dosage of all psychotropic drugs should be done gradually and carefully monitored. Increasing dosage to previous levels is necessary at the first sign of recurrence of the target symptom. If reduction of dosage is not successful, reduction should be attempted again at increasing intervals. In general, there is a tendency to spontaneous remission for most of the target symptoms for which psychotropic drugs are prescribed so that in time the drug will no longer be necessary. If the patient is depressed because of loss of memory as a result of senility, he will adjust in time or lose his awareness of the deficit with the progression of his memory loss. Very few elderly patients who have functioned in the community until old age need to be maintained on psychotropic drugs for the rest of their lives.

Electroconvulsive therapy (ECT) is still very useful in elderly patients with severe depressions characterized by either markedly decreased or markedly increased motor activity. Success is both more likely and more rapid with electroconvulsive therapy than with antidepressant medication or psychotherapy in the treatment of these patients. Eighty-five to 90 per cent of such patients with illness of recent onset will improve after a course of 6 or 8 treatments. There will be a transient organic brain syndrome that will clear after several weeks.

To paraphrase Osler, in treating the elderly patient with changes in behavior, mood, or thinking, the physician can sometimes cure, can often relieve, and can always comfort. The physician treating these patients needs diagnostic acumen, optimism, an interest in the elderly and their problems, and an awareness of how to use major tranquilizers and antidepressants.

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Coney Island Hospital
2601 Ocean Parkway
Brooklyn, New York 11235

Aging and the Extrapyramidal System

Barbara A. L. Beasley, M. D., and Donald H. Ford, Ph.D.***

With advancing age, certain neurologic signs occur so often that they are considered to be normal in the senium. They represent the composite of changes that have taken place with the aging of the nervous system and are frequently manifest as a predominant extrapyramidal syndrome that is not unlike that seen in Parkinson's disease.[6,2] The major features are rigidity, hypokinesia, and flexed posture. It has also become evident that in parkinsonism, dementia and signs of frontal lobe dysfunction with cortical atrophy (especially of the frontal lobe) develop. The magnitude of these changes is probably greater than one would expect for an individual of the same age without Parkinson's disease.[1,9] These facts lead one to wonder whether the neuropathological changes seen in the senium and Parkinson's disease do not represent a spectrum of a degenerative process. Careful clinicopathological correlations for such observations are yet to be made.

Other extrapyramidal signs and symptoms, including chorea and tremor,[6] are seen frequently enough in the senium to warrant discussion. These may also represent variations of such a degenerative spectrum.

The anatomic, physiologic, biochemical, and pathologic aspects of extrapyramidal diseases are incompletely understood. What is known deserves a short simplified review.

Anatomy

The terms "basal ganglia" and "extrapyramidal system" are entrenched and confused in the neurologic literature.[8] They have come to mean subcortical nuclear masses that influence motor function. As used today, the term "basal ganglia" does not include all the classical basal ganglia and in addition includes other structures that are neither part of this classic group nor located in the basal ganglia region. The classic extrapyramidal system (tectospinal, rubrospinal, vestibulospinal, and reticulospinal tracts) exists in parallel to the pyramidal motor system. Both the extrapyramidal and pyramidal systems are influenced by the subcortical nuclear masses. These nuclear masses include the striatum,

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*Associative Chief of Neurology, U.S. Public Health Service Hospital, Staten Island; Assistant Professor of Neurology, State University of New York, Downstate Medical Center, Brooklyn, New York

**Professor of Anatomy, State University of New York, Downstate Medical Center, Brooklyn, New York

the subthalamic nuclei (corpus Luysii), and the substantia nigra. The neocerebellum is also sometimes included.

The striatum,[4] substantia nigra, and subthalamic nuclei are largely responsible for normal stereotyped involuntary motor activity and are influenced by the cortex. They function through a feedback loop between themselves and the cortex via the thalamus (Fig. 1). The corpus striatum is divided phylogenetically into two parts, the first of which is the paleostriatum or globus pallidus which is situated more medially. It is the older part and remains as the principal efferent pathway or outflow of the basal ganglia nuclei into which the more recently added nuclei feed. It sends its major fibers to the thalamus. The newer part, or neostriatum, is located lateral to the paleostriatum and is composed of two parts, the caudate and the putamen, which are of similar histologic composition and function, and are divided by the traversing fibers of the internal capsule. Both of these nuclei send most of their efferent fibers to the paleostriatum.

The substantia nigra (with its melanin-pigmented cells) is situated dorsal to the cerebral peduncles of the midbrain. It sends fibers to the corpus striatum. The subthalamic nucleus, situated in the subthalamus medially and adjacent to the internal capsule, also sends its efferent fibers predominantly to the globus pallidus.

The circuitry of the basal ganglia can best be viewed as a feedback loop with the globus pallidus being the major outflow or efferent nucleus, and the cortex feeding back into the basal ganglia to complete the loop.

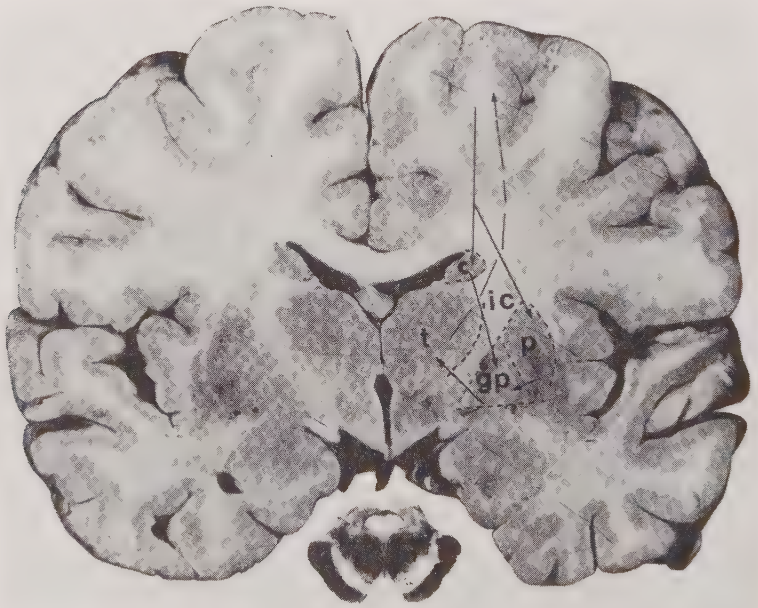

Figure 1. Schematic representation of basal ganglia pathways. t, thalamus; gp, globus pallidus; c, caudate; p, putamen; sn, substantia nigra, ic, internal capsule.

The major output of the globus pallidus goes to the thalamus (ventral anterior and ventral lateral nuclei) which in turn sends fibers to the cortex (predominantly the motor and premotor cortex). "Extrapyramidal dysfunction" may be caused by the loss of any one of the structures or the "release" of remaining structures anywhere within this feedback loop or outside it.[9]

Pathology

Idiopathic Parkinson's disease is associated with diffuse cortical atrophy (especially the frontal lobes) and diffuse degeneration of the melanin-containing neurons of the brain stem.[9] Although symptoms of parkinsonism occur following cell loss in the substantia nigra, it is not known which of the other more widely spread lesions seen in Parkinson's disease or which of the surviving undestroyed structures produce these symptoms.

Parkinson's disease is confusing because many pathologic entities cause parkinsonian syndromes, and because the etiology of idiopathic Parkinson's disease remains obscure. Three clinicopathologic forms of parkinsonism are recognized in addition to the idiopathic type. They are arteriosclerotic parkinsonism caused by multiple cerebrovascular accidents, post-encephalitic parkinsonism, and parkinson-dementia amyotrophic lateral sclerosis. Other causes of parkinsonian symptoms include carbon monoxide poisoning, magnesium poisoning, and Wilson's disease. Parkinsonian symptoms also frequently accompany aging of the central nervous system. These facts suggest the following questions: (1) Are idiopathic Parkinson's disease and aging variations in a spectrum of a degenerative process? (2) Are there other entities included in this spectrum? (3) Are we simply dealing with multiple entities causing similar syndromes depending on their location and extent?

The causative pathologic lesions underlying the "extrapyramidal" features in the aged are unknown. Although pathologic changes have been found in the "basal ganglia" of aged patients, [2,1,9] no study has been done to correlate the pathologic findings seen in clinically examined aged patients with and without parkinsonian extrapyramidal signs and symptoms. Most specifically, quantitative cellular changes (size, type, and number) need to be determined. The biochemical changes noted are likely to be secondary to the structural pathologic changes.

Biochemistry

With the discovery that dopamine, a neurotransmitter, is in high concentration in the neostriatum, and that it is selectively depleted in these structures in parkinsonism, a search for a biochemical basis of "basil ganglia" and related diseases was begun. Dopamine is formed in the pigmented cells of the substantia nigra as well as in their neuronal terminals. It is an inhibitory neurotransmitter for most striatal neurons.[10,15] Currently, parkinsonism is considered as a striatal dopamine deficiency syndrome.[10]

Dopamine is probably counterbalanced by the predominantly excitatory neurotransmitter acetylcholine, which appears to remain unaltered in parkinsonism. It is therefore believed that in parkinsonism, cholinergic effects predominate because of reduced dopaminergic activity.[10,19] Such a balance between inhibitory and excitatory systems is comparable to the balance which exists between the sympathetic and parasympathetic autonomic nervous systems. This balance between cholinergic and dopaminergic activity seems all the more likely since anticholinergic agents have a therapeutic value in treating parkinsonian symptoms.

Gamma amino butyric acid (GABA), a putative neurotransmitter, is reduced in brains of patients with Huntington's chorea, and speculation as to its function in chorea and more generally in all movement disorders is being investigated.[17] Further, GABA may have some role in the integration of functions between the substantia nigra and the striatum since it has been observed that striatal neurons projecting to the substantia nigra contain GABA.[14]

Serotonin, another amine, is found in appreciable quantities in the striatum. However, its role is not yet known.

The precise role of dopamine in the striatum is to a degree confusing because at the onset of treatment of parkinsonism with levodopa (the dopamine precursor used in therapy because it can pass the blood-brain barrier) and with long term therapy, some patients develop choreiform movements. Similarly, choreiform movements in nonparkinsonians are often successfully treated with drugs that deplete dopamine or block the dopamine receptors, and these drugs can themselves produce parkinsonian symptoms. These drugs can also produce chorea in patients when their dose is decreased precipitously or if they are given for a long period of time. These observations demonstrate the complex balance of the neurotransmitters within the central nervous system and the incomplete state of our knowledge.

In the aged, quantitative changes in certain of the catecholamines and their metabolites occur. Specifically, a significant reduction of dopamine and its metabolites has been noted.[2,5] There is also a reduction in glutamic acid dehydrogenase (GAD), the enzyme which decarboxylates glutamic acid to form GABA.[5] In addition to the actual changes in neurotransmitters, there is some evidence that there may also be alterations in the receptor sites for these neurotransmitters.[18]

Although levodopa and other medications which are related to neurotransmitters have proved to be effective in the treatment of movement disorders by altering the neurotransmitter balance toward a more normal state, the basic pathological problem seems to be structural. With a gradual loss of cells, multiple neurotransmitter systems have deteriorated, making replacement treatment difficult if not impossible.

Physiology

Without a biochemical, anatomic or pathologic understanding of "basal ganglia" disorders, the physiologic basis can hardly be grasped. Accordingly, the terminology used for disorders of the "basal ganglia" has been descriptive. The general term for such disorders is "Movement Disorders," and the different types are named according to either their speed or form of movement. Such terminology leaves one with very little understanding of the pathophysiology.

One physiologic approach to these disorders, described by Martin,[12] has the advantage of giving these disorders a common functional basis. He looks at movement disorders as a group of disorders of postural reflexes that are controlled by the subcortical nuclei. These reflexes maintain posture of the body during movement of the body itself or of its supporting base. They include such reflexes as those for normal posture of the body, for protection against falling, for normal locomotion and for rolling over in bed or getting up out of a chair. Man with his narrow base and high center of gravity (first sacral vertebra) is particularly in need of these reflexes, as evidenced by the frequent falls, abnormal postural changes and locomotive difficulties of patients without them such as those with "basal ganglia" disorders.

Similar postural changes are seen in patients with loss of the vestibular, somatic proprioceptive and visual sensory systems, suggesting that integration of these sensory systems might be impaired in patients with "basal ganglia" disease.[12]

These postural reflexes can become excessive, perhaps by "release" or loss of inhibition, producing positive symptomatology. This can be of the kinetic type, as in hemiballismus or chorea, with an excessive response to instability of the supporting base, or of the static type, as with rigidity. If these reflexes are diminished, one sees negative symptomatology such as disorders of righting, locomotion, or posture.

As these "basal ganglia" postural reflexes are active only during movement of man or of his supporting base, the symptoms of "basal ganglia" disorders are absent when these patients are asleep or completely at rest.

PARKINSONIAN OR AKINETIC HYPERTONIC FEATURES OF THE AGED

The clinical neurologic expression of the aged person is strongly reminiscent of the parkinsonian with the exception of resting tremor, which may be present but is not a frequent clinical finding. Other parkinsonian features such as flexed posture, rigidity, and akinesia are clearly evident in the elderly.[6,2,12] Even the expert often finds it difficult to distinguish elderly patients with parkinsonian features from those with Parkinson's disease. This overlap of clinical findings again suggests that we are dealing with a spectrum of degenerative entities.

Other syndromes to be excluded in patients with hypokinesia and rigidity include drug-induced parkinsonism (butyrophenones and phenothiazines), normal pressure hydrocephalus, the spastic gait of cervical spondylosis, and rarer disorders such as Shy-Drager syndrome, supranuclear opthalmoplegia, and striatonigral degeneration.

Posture

The posture of the aged is one of general flexion. The head is bent forward on the neck. The upper extremities are flexed at the elbows and the wrists with the thumb held in apposition, while the lower extremities are slightly bent at the hips, knees, and ankles. Even on reclining, a supine aged patient often continues to maintain flexion of the neck so that his head remains off the pillow. If told to stand straighter, he will erect himself voluntarily for a moment only to resume his previous involuntary stance thereafter. Of course, aging changes of the joints and ligaments must also be taken into account since these produce fixed flexion.

Rigidity

The muscular rigidity of the aged, often referred to as gegenhalten ("opposition") or paratonia, is reminiscent of cogwheel rigidity of the parkinsonian. Its mechanism, like cogwheel rigidity, is poorly understood. Unlike cogwheel rigidity, it is inconstant, increasing with greater rapidity of passive manipulation of the limb and counter force and often more marked in the legs than the arms.

Hypokinesia

Another extrapyramidal feature common to Parkinson's disease and aging is poverty of movement with loss of associative movements such as arm swinging. Both the aged person and the parkinsonian lack the normal frequent crossing and uncrossing of legs, fidgeting with the hands, and change of ocular gaze. The eyes rarely blink, and the face tends to be immobile.

Gait

The gait of the elderly (frontal lobe apraxia) is considerably impaired and similar to but not exactly like that of the parkinsonian. It is frequently wide-based and tends to exaggerate flexion posture. Often these patients tumble forward if they walk rapidly (propulsion), or they may fall backward (retropulsion). Initiation of walking is particularly difficult and is often preceded by an inefficient foot shuffle referred to as the "slipping clutch" gait. The feet appear to stick to the floor, prompting the descriptive term "magnetic gait." In enclosed areas, these patients often freeze, as do parkinsonians, because of increased visual contact from the enclosing surroundings.

With time, the gait of many parkinsonians becomes more like that of the aged, with "sticking feet" as a prominent feature. In our experience, levodopa, rather than alleviating this problem, may increase the tendency to "sticking feet."

Contactual Difficulties

Both the parkinsonian and the aged patient can manifest contactual symptoms. They can be elicited by touch and/or visual stimulation. Their mechanism is unknown. Difficulty turning over in bed or getting out of deep chairs is due to an excessive contactual response to touch. The greater the surface area of contact, the more difficulty these patients have in indulging themselves. Small areas or doorways cause these patients to freeze because of increased visual contact. These contactual difficulties can be effectively counteracted by counter contact (touch or visual). For example, one can easily draw these patients up and out of chairs by guiding their movements (visual contact).

Table 1. *"Frontal Lobe" Release Signs*

Grasp reflex	hand grasping of an object that stimulates the palm
Tonic foot response	tendency for the toes to turn down (cupping of the foot) when the ball of the foot is stimulated.
Oral responses	elicited by perioral stimulation of the skin: Sucking reflex, rooting reflex, snout reflex
Palmomental reflex	unilateral contraction of the mentalis muscle with stimulation of the ipsilateral thenar eminence of the hand
Corneomandibular reflex	ipsilateral strong blink and contralateral movement of the chin with corneal stimulation
Glabellar tap reflex	failure to inhibit continued blinking with repetitive tapping over the glabella

"Frontal Lobe" Release Signs

These reflexes (Table 1) are often prominent in the senium, and they may or may not be associated with intellectual loss. Although they are undoubtedly caused by neuronal loss, the same reflexes are present in infancy and are felt to disappear with development of the central nervous system's cortical inhibition. Accordingly, with degeneration of the central nervous system, cortical inhibition is diminished, and these signs reappear. These reflexes have been observed especially in patients with frontal lobe lesions and are a frequent finding in parkinsonians. Again, it is tempting to speculate that neurologic changes seen in the aged and in Parkinson's disease are variations in a spectrum of degenerative diseases.

Treatment

Unfortunately treatment is less effective in aged patients with hypertonic, akinetic abnormalities than in true parkinsonian patients. The former are also more apt to develop central nervous system side effects with levodopa and other anti-parkinsonian agents. These side effects consist of confusional states, agitation, and involuntary movements.[3] It should be emphasized that the recently released drug Sinemet (L-dopa plus the peripheral decarboxylase inhibitor that inhibits the breakdown of levodopa outside of the central nervous system) delivers approximately five times as much L-dopa to the neostratium as would be delivered without the decarboxylase inhibitor despite its apparent lower dose of L-dopa. The side effects of involuntary movements and mental changes are more common with this medication than with levodopa alone.

CHOREA AND THE AGED

Chorea seen in the aged is associated with several syndromes, including buccal-lingual-facial dyskinesia (BLFD) and senile chorea.[18] These two entities probably represent a spectrum of progressive degeneration of the striatum and cortex. BLFD in the aged consists of repetitive, involuntary movements of the tongue, lower facial muscles, and jaws or masticatory muscles. They appear as pouting, chewing, and puckering of the lips. Such mouthing movements can also be induced by long term neuroleptic treatment (phenothiazines and butyrophenones), but occur in the aged without such treatment. BLFD unassociated with an identifiable extrapyramidal syndrome and in persons not receiving any neuroleptic drug therapy is more common in the elderly than senile chorea.

Senile chorea is a syndrome consisting of symmetric, involuntary movement, especially of the distal part of the extremities and buccal-lingual-facial muscles. It is slowly progressive. In order to make this diagnosis, one must exclude Huntington's chorea, which is familial, and vascular accidents, which have a sudden onset.

Pathologic examination of brains of patients with BLFD in the aged has not revealed striking findings. Pathologic examination of brains of patients with senile chorea has revealed findings similar to but less extreme than those with Huntington's chorea. Both are associated with marked degeneration of cells in the caudate and putamen as well as in the cerebral cortex.

It has been suggested that BLFD in the elderly may represent the earliest manifestations of senile chorea. This implies that the area of the striatum topographically related to the face is first to develop dysfunction. Biochemically, these choreiform syndromes are felt to be due to an altered dopaminergic system within the striatum. Anticholinergic drugs and agents that increase central nervous system dopamine concentration such as L-dopa, Sinemet, and Amantadine exacerbate chorea while agents that reduce central nervous system dopamine effect decrease choriform movements. Although L-dopa produces chorea in parkinsonians and increases chorea in patients with chorea, it does not produce chorea in normal individuals. It has, therefore, been postulated that the abnormality in these syndromes is at the dopamine receptor sites in the striatum.

Treatment

Pharmacologic blockade of dopaminergic receptor sites or depletion of dopamine is the only effective way to treat patients with BLFD and senile chorea syndrome. However, such treatment should not be given unless the movements are disabling, since long term use of these drugs can elicit analogous disorders as well as parkinsonian symptoms. The drugs usually given are haloperidol (1 mg tablet) or chlorpromazine (25 mg tablet). One begins therapy with a small amount—one tablet twice daily—and gradually increases the dose until symptoms are alleviated. Anticholinergic drugs tend to exacerbate the movements and should not be used.

TREMOR

Tremor is not a common feature of old age.[6,7,11] It is most frequently a postural tremor (one that occurs when the affected part of the body is actively maintaining a posture). It is called senile tremor and is synonymous with essential, familial, or hereditary tremor that has developed or become apparent in late life. This tremor is coarse. It is accentuated by stress and relieved with alcohol. It usually increases with voluntary movement and may exist also at rest. Because of these features, it is frequently confused with the static tremor of Parkinson's disease or the action tremor of cerebellar disease, though other cerebellar signs such as ataxia and nystagmus are lacking. Its pathophysiology is unknown. Patients present with unsteady hand movements, tremulous speech, and shaking of their heads (titubation).

Therapy is often unsuccessful. Beta adrenergic blockers such as propranolol reduce the amplitude but not the frequency of the tremor. Dramatic effects are seen in only about 10 per cent of patients, but some improvement is seen in 66 to 79 per cent. Propranolol is given in a dose of 30 to 40 mg three times daily. Rarely is stereotaxic surgery indicated. Tranquilizers and sedatives such as diazepam and barbiturates may be helpful during periods of stress.

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Department of Neurology
U.S. Public Health Service Hospital
Staten Island, New York 10304

Preventive Medicine in Geriatrics

*Seymour M. Glick, M.D.**

The term preventive medicine in the conventional sense usually conjures up a vision of prenatal care, infant care, or immunization of young people. Geriatrics is possibly the least likely area to be associated in the minds of most physicians with preventive medicine. Yet, an excellent case can be made not only for the viewpoint that preventive medicine is equally important in dealing with the elderly, but that it actually may be more critical and life-saving in this population of patients. Any physician dealing with acute hospital care of the elderly, with its attendant high mortality, cannot help but be impressed with the large number of patients coming to the hospital at a stage beyond help; yet these elderly individuals clearly might have been saved and restored to useful life and/or prevented from reaching the acute decompensated stage by timely preventive measures.

In the geriatric population, prevention is generally not "primary prevention," that is total prevention of disease, but rather "secondary prevention," or prevention of the deterioration of an existing condition. The distinction between prevention and early treatment is necessarily and appropriately blurred. Since the elderly patient is more fragile than his younger counterpart, and relatively trivial breakdowns in homeostasis can have irreversible and often fatal consequences, prevention is of greater importance in this age group—from the point of view of the serious consequences resulting from the failure to apply timely prevention.

The average physician, trained as he is in a narrow definition of medical care, in the direct physician-patient, one-to-one interaction and in the treatment of physical illnesses, and taught to savor the instant gratification of miracle drugs and rapid cures, is ill equipped educationally and temperamentally to cope with the exigencies of geriatric preventive medicine and to derive the appropriate professional satisfaction from its application. Just as the process of emotional maturation from childhood to adulthood involves broadening of one's horizons and learning how to trade instant gratification for long-term gains, so too the physician must learn to grow professionally in his or her concept of professional satisfaction if he or she is to do justice to the ever-growing elderly population.

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*Professor and Chairman, Department of Medicine, Ben Gurion University of the Negev; Health Sciences Center; Chief, Division of Medicine, Soroka University Hospital, Beersheva, Israel; Formerly Chief of Medical Services, Coney Island Hospital, Brooklyn, New York

In her beautiful and comprehensive book *Coming of Age*, Simone de Beauvoir[1] provides a panoramic view of aging throughout many eras and in different cultures. The diversity of attitudes and approaches is instructive, but no ultimate escape exists from the deterioration of physical, social, and mental function associated with the aging process, whether in mid-Manhattan or on Samoa. Gerontologists may continue their search for the fountain of youth, but even were they to succeed, it is unlikely that they could do more than merely postpone the inevitable a bit longer, "buy some time." It is the physician's responsibility to make this period of life as healthy and satisfying for the patient and society as is possible within the limited potential available.

The problems of the elderly are often largely economically conditioned. The kind of medical, nursing and rehabilitative care available for Joseph P. Kennedy, Sr., following his stroke is simply unavailable in quality and quantity to most elderly. This economic handicap may be reflected in a shortened life and in a more deprived, lonely, and unhealthy final period of life. In the United States, in spite of Social Security and Medicare, millions of elderly Americans, whose long years of work did not reward them with adequate pensions, suffer medically because of financial straits. These difficulties result in inadequate dentures, hearing aids, reading glasses, and nutrition, and perhaps equally important, in impaired mobility. The elderly couple who can afford to travel, to go to the theater, and to visit friends can stave off the vicious cycle of boredom, depression, and isolation that leads to poor nutrition, neglect of serious medical conditions, and ultimately to serious ill health and death. The thoughtful physician must consider his responsibilities to the elderly in terms of economics, housing, transportation, and recreation as well as in the more conventional terms of drugs and hospitalization. That is not to say that the physician is to abandon his traditional role and to become largely a "do gooder," merely a social reformer. But on the other hand, for the physician blithely to continue to wallpaper cracks in the structure of his patient's health while the entire edifice is collapsing around him borders on the absurd and irresponsible.

In dealing with the health problems of older people, the physician must also be aware that the older person is less likely to present himself or herself to the physician with these problems than is the younger person,[6] and that the problems must therefore be actively sought. The failure of the elderly to seek help is multifactorial. Firstly, like physicians and others in their society, they have already been erroneously conditioned to attribute potentially serious complaints to "aging." The constipation of the hypothyroid individual, and the nocturia of the obstructing prostate are all too readily dismissed by the patient because of previously appreciated attitudes of the physician. Secondly, the elderly often have associated depression or other mental impairment which robs them of initiative and of the will to act expeditiously and in a timely manner. In addition, there are a host of other reasons, including lack of mobility, lack of money, embarrassment, decreased sensitivity to pain, which lead to self-neglect of the elderly until disease processes progress irremediably. The medical community must, therefore, *seek out* preventable illness in the aged if it is to do justice to the myriad problems of this age group.

Case finding need not be carried out exclusively by the physician. Indeed, in most circumstances it is impractical for the physician to carry out this function. Furthermore many of the ultimate preventative and therapeutic regimens are not medical, but involve a spectrum of community social and health services. It is therefore essential that the physician learn to work as a member of a health team and that he delegate or leave to others those tasks for which they are better trained and temperamentally better suited and restrict himself to those areas in which his training and expertise are unique. Specially trained geriatric nurses exist in a few places throughout the world and can probably play a major role in early disease detection and prevention.

In areas of what might legitimately be called prevention, the physician might address himself to several of the following aspects of geriatric care:

SOCIALIZATION. The elderly must avoid isolation. Those who can perform useful work, whether for pay or as volunteers, should be encouraged to do so. Many opportunities are available for retired people to make important societal contributions and simultaneously derive considerable benefit. These activities prevent mental deterioration and depression and preserve a reason for living, so vital to the elderly. The physician, or members of his team, should be aware of each community's opportunities for utilizing the services of the aged and bring these to the attention of his patients. For those elderly who are more limited, arrangements for frequent visitors or a "buddy system" should be worked out to prevent loneliness and isolation with their consequent deterioration.

PHYSICAL ACTIVITY. A program of regular, graded physical activity and exercise within the capabilities of the individual has much to recommend it. Such a program has both physical and psychological benefits far beyond its direct benefits. The physician must be cautious to select a program compatible with the physical and temperamental capabilities of his patients. Early ambulation after operations and illnesses falls under this category and is essential in management of old people.

NUTRITION. In our wealthy society the elderly are perhaps the most commonly seriously undernourished segment of the population. The causes for malnutrition are economic, educational, dental, and mental, but the results are similar, whatever the cause. A nutritional survey of the diet of each patient, plus remedial education with respect to nutritional requirements can be helpful. "Meals on wheels" to infirm and homebound elderly are available in many communities, though physicians are often unaware of them.

PREVENTION OF ACCIDENTS. One of the classic modes of exitus for the elderly is the fractured hip with its sequelae: indwelling catheter, bed sores, pulmonary embolization, and bronchopneumonia. In colder climates the dangers of ice and snow should be highlighted. Everywhere the most dangerous place is at home, with ladders and chairs often the ultimate death weapon for the elderly prone to vertigo. Burns, injuries to extremities with compromised circulation, and inadvertent poisonings are common enough to require thoughtful, prophylactic attention and instruction. In some parts of the world, space-heaters are a common, quiet cause of death and disability. Their use must be carefully regulated.

PREVENTION OF IATROGENIC DISEASE. With several bodily systems often affected by disease and the resultant multiple complaints, it is often tempting to resort to the symptom-pill reflex. This common reflex, hazardous at all ages,[4] is much more dangerous in the elderly. A cautious, conservative approach to medications may be one of the physician's most valuable contributions to the life and health of his elderly patients. Among the drugs most commonly causing serious problems are the diuretics, with their enervating volume and electrolyte depletion; reserpine, with its insidious depression; digoxin, with its unpleasant gastrointestinal effects but deadly myocardial impact; and the oral hypoglycemic agents, with their central nervous system hypoglycemic propensity. The elderly are more sensitive to drugs; their kidneys and liver excrete and metabolize the drugs more poorly, and their tissues may be more sensitive to the drug effects. The ill effects are often magnified and the elderly patient recovers more slowly from setbacks.

Similarly, the avoidance of mutilating and dangerous surgery in the elderly is often well-advised when one considers the patient in toto rather than the welfare of an organ or organ system.

FOOT CARE. Careful instruction with respect to daily attention to the feet is perhaps the most important facet of instruction to the diabetic patient and one of the simplest, yet most beneficial steps for all elderly patients. Fragile skin in an extremity poorly supplied by a deficient blood circulation and poorly protected by a hyposensitive nerve supply is vulnerable to injury and ulceration. Ulcers are infinitely harder to heal than to prevent. Daily inspection, washing, drying, and anointing of the feet and periodic visits to the podiatrist are an essential facet of geriatric preventive medicine. Surveys have shown that 70 per cent of the "healthy" elderly are in need of podiatry.[2]

ELIMINATION OF SMOKING. While it is unlikely that cessation of smoking in the elderly can be effective in relieving their subsequent incidence of lung cancer, this simple maneuver is effective in other illness even over the old person's few remaining years of life. Particularly important reasons for stopping smoking include reduction in the incidence of lower respiratory tract infections, their severity and complications, the decreased danger of peripheral vascular disease, and the beneficial effect on the heart. In spite of the frequently voiced argument that smoking may be one of the few pleasures left to the elderly, the objective harmful effects of smoking do not justify such complacency.

IMMUNIZATIONS. The vulnerability of the elderly to influenzal complications argues for the routine immunization of the elderly in years of impending influenza epidemics in accordance with the recommendations of the United States Public Health Service.

DETECTION AND PREVENTION OF CANCER. The routine of early cancer detection, particularly in those areas of the body in which the prognosis for early detection is good and the detection techniques relatively simple and benign (rectum, cervix, breast), is worth following.

Preservation of Sight and Hearing. The rapid downhill course characteristic of the senile individual is often directly traceable to sensory deprivation resulting from the gradual loss of vision and hearing. Regular ophthalmologic and audiometric evaluation should be carried out. The physician should be aware of his responsibilities in the prevention of blindness from glaucoma, temporal arteritis, cataracts, and possibly that from diabetic retinopathy. These conditions are amenable to therapy, and some of them will progress rapidly to irreversible blindness if not treated. Hearing loss, often remediable by hearing aids or surgery, is even more insidious and may present as a character change and as mental deterioration, rather than as a complaint of deafness.

Preservation of Myocardial Compensation. The huge population of elderly cardiac patients is generally treated quite well with diuretics and digitalis preparations. But these patients are often readmitted to the hospital repeatedly with recurrent pulmonary edema caused by salt overload. Dietary instruction by most physicians is poor, understanding of the instructions given is poorer, and adherence by patients is worst of all. Periodic house visits by a dietitian or a trained health worker to actually observe what the patient is cooking is an ideal to be sought and can be life-saving. Among the kinds of dietary indiscretions most common among the elderly is the use of canned soups as a warm, cheap, and tasty meal. The canned soups contain enormous quantities of salt, not appreciated by the patients and rarely asked about by the physician. Various ethnic foods not appearing on the "forbidden lists" are often eaten innocently with dire consequences. Even so simple an instruction as the taking of an extra dose of a diuretic prior to a wedding meal or other impending dietary indiscretion can be most helpful in reducing the incidence of pulmonary edema. Daily weighing is another simple preventive measure.

In contrast to the importance of a low salt diet, the emphasis on low cholesterol or low saturated fat diets in the prevention of heart disease is likely to be a waste of time and effort unless it is meant to be a form of occupational therapy or placebo, because the time scale of effectiveness is so long as to preclude its usefulness in the elderly.

Several other important measures in the prevention of deterioration of heart function are care in the use of cardiotoxic drugs, both those with positive inotropism (digitalis) and negative inotropism (propranolol) and the effective treatment of hypertension.

Preservation of Renal Function. The focus in the elderly should be the detection and treatment of urinary tract obstruction, prevention of infection, and avoidance of nephrotoxic drugs and unnecessary bladder catheterization. Impaired urinary flow secondary to benign prostatic hypertrophy in men, gynecologic disease in women, and insidious diabetic neuropathy of the bladder should not be forgotten as possible primary causes of any azotemia or as contributory factors to the worsening of pre-existing azotemia of any etiology.

PULMONARY FUNCTION. Pulmonary function can best be preserved by total elimination of smoking, and by prevention and prompt treatment of upper respiratory infection. The latter is best accomplished by avoidance of unnecessary exposure to individuals with respiratory infections, by immunization against influenza, and by physical measures in the postoperative period. Individuals with chronic obstructive lung disease often benefit by courses of antibiotics periodically throughout the winter.

NEUROPSYCHIATRIC FUNCTION. Preservation of neuropsychiatric function can best be achieved by a two pronged approach: medical and social. Prevention of organic deterioration is basically a composite of health maintenance in every sphere of bodily health because decompensation in any area of physical function quickly reflects itself in a deterioration of cerebration. Fever, drug intake, pulmonary decompensation, cardiac decompensation, liver and renal failure, a variety of endocrine dysfunctions, and anemia are a few of the many categories of disease which may be the treatable causes of "organic brain syndrome."

The other facet of neuropsychiatric function is the social aspect. Those individuals who have led an active, intellectually alert and diverse life are likely to be blessed with better preserved intellectual function. A variety of outside interests and activities and a purpose to their life are vital aspects for preservation of healthy mental and emotional function in the elderly. Continued sensory input from the outside world is vital for continued mental effectiveness. Deterioration of neuropsychiatric function often dates from loss of a companion, from confinement to home by illness, or from hospitalization, with its threatening severance from a familiar and secure life pattern. At these times of potential crises, provision of substitutes for the supportive elements which are taken from the patient can be helpful in preventing the anticipated deterioration. Thus a friend at the bedside, frequent visits, and positive stimulation are very helpful.

GASTROINTESTINAL FUNCTION. It is often forgotten that this system starts with the mouth; well fitting dentures, or teeth in good repair, are critical elements for a well functioning individual who can preserve his nutrition and his positive frame of mind. This area of the body is often neglected by the otherwise conscientious physician and is very commonly impaired—often because of economic constraints. A recent survey[3] revealed need for dental care in two thirds of the elderly examined. The wearing of dentures by a patient on a visit to the physician may mean only that the patient has a cosmetically adequate set of dentures, but should not lull the physician into ignoring the question of adequacy of dental function in his history and physical examination.

Focus by the elderly on gastrointestinal excretory function is often regarded as a petty annoyance by the physician. This attitude must not cause the physician to overlook subtle changes in bowel habit and digestion with potentially serious consequences.

ANEMIA. Anemia is a common, usually treatable, deviation from the norm which may be a clue to a more important basic derangement of bodily function—whether an occult bleeding site, a cause of malnutrition, or a hidden infection. The clue of anemia should alert the physician to his role in preventing further deterioration of anemia and of the basic underlying condition. The temptation to use "shotgun" anti-anemia therapy rather than proceed to an often inconvenient and expensive work-up in the elderly is a dangerous, though seemingly expedient, approach and is to be deplored.

While much of the above discussion has been organ or system oriented, the elderly are characterized by simultaneous disease in multiple systems of the body,[6] and require a broadly based approach. More important is the understanding by the physician of the vicious cycle of interrelated diseases in the elderly. The obesity, which stresses the heart, causes the patient to be immobilized, thereby impairs bladder emptying, leading to azotemia and obtundation, resulting in bronchopneumonia, further straining the heart. These interrelationships, present in medicine at all ages, are more obvious and important in preventive geriatrics because of the limited reserve of each organ system.

In addition to the importance of progressing beyond an organ or system oriented approach to a view of the total patient, a geriatric perspective requires a functionally oriented approach. It is esential to base one's assessment of elderly individuals in terms of their ability to function independently in each of the important spheres of daily living. A patient who is otherwise reasonably healthy but who because of a recent hospitalization has elected to remain bedridden cannot be thought of merely in terms of the physical deficits which exist, but must be viewed in terms of what can be done to restore the individual to a satisfactorily functional state.

In all programs of preventive geriatrics, since resources are usually limited, it is well to recognize the populations at high risk and to concentrate one's efforts on those groups. These groups include the homebound, those living alone, those recently bereaved, those with mental impairment, those recently discharged from a hospital, and those with significant locomotive difficulty.[5]

The preventive approach is excellent for the patient. It also has much to recomend it from the point of view of the physician and his personal satisfaction. One often hears of the tedium of routine check-ups as typified in practices frequented by well-to-do, relatively young and healthy people. In the elderly, such "routine" examinations, if performed with appropriate consciousness of the benefits to be derived from such surveys, can be exciting exercises. It would be rare for an alert physician to be unable to uncover some facet of his elderly patient's life to which he cannot make a significant contribution. There are few other areas of daily office medicine which can make that claim.

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Department of Medicine
Central Negev Hospital
Beersheva
Israel

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